1,2-Benzisothiazol-3(2H)-one, 2-butyl (BBIT)
Final Work Plan

Registration Review: Initial Docket
Case Number 5017

September 2016

Approved by: _____

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Date: 9/20/16

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TERMS, ABBREVIATIONS AND SYMBOLS

AD	Antimicrobials Division
A.I. or a.i.	active ingredient
aPAD	acute population adjusted dose
ASRI	activated sludge respiration inhibition
atm-m^3/mole	atmospheric pressure-cubic meter per mole
BCF	bioconcentration factor
BBIT	1,2-Benzisothiazol-3(2H)-one, 2-butyl
°C	degrees Celsius
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CMA	Chemical Manufacturers Association
CO_2	carbon dioxide
COC	concentration-of-concern
cPAD	chronic population adjusted dose
DCI	data call-in
EC_{50}	median (or 50 percent) effect concentration
EC_{05}	5 percent effect concentration
ECOTOX	ECOTOXicology
EDI	estimated daily intake
EDSP	Endocrine Disruptor Screening Program
E-FAST	Exposure and Fate Assessment Screening Tool
EPI Suite	Estimation Program Interface Suite
EPA	Environmental Protection Agency
ET	Extrathoracic
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
FWP	Final Work Plan
g/mol	grams per mole
GLN	guideline number
GSD	Geometric Standard Deviation
HEC	Human Equivalent Concentration
HPV	high production volume
IDS	Incident Data System
Koc	organic carbon normalized soil-water partition coefficient
Kd	soil-water partition coefficient
Kow	octanol-water partition coefficient
LC_{50}	median (or 50 percent) lethal concentration
LD_{50}	median (or 50 percent) lethal dose
LOAEC	lowest-observed-adverse-effect-concentration
LOEC	lowest-observed-effect-concentration
LOAEL	lowest-observed-adverse-effect-level
Log K_{ow}	logarithm of the octanol-water partition coefficient
µg	microgram
ml/g	milliliter per gram
mg/kg	milligram per kilogram

mg/kg/day	milligram per kilogram per day
mg/L	milligram per liter
mm Hg	millimeter of mercury
MMAD	Mass Median Aerodynamic Diameter
MOE	margin of exposure
MRID	Master Record Identification Number
MRL	maximum residue limit
N/A	not applicable
nm	nanometers
NOAEC	no-observed-adverse-effect-concentration
NOAEL	no-observed-adverse-effect-level
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organization for Economic Co-operation and Development
OPP	Office of Pesticide Programs
PAD	population adjusted dose
PAI	pure active ingredient
PDM	Probabilistic Dilution Model
%	percent
PC Code	Pesticide Chemical Code
PCF	pounds per cubic foot
pH	power of hydrogen or power of the concentration of the hydrogen ion
PHED	Pesticide Handler's Exposure Data
PIS	primary irritation score
pKa	power of the acid dissociation constant or negative base-10 logarithm of the acid dissociation constant of a solution
ppb	parts per billion
ppm	parts per million
PWP	Preliminary Work Plan
QSAR	quantitative structure-activity relationship
RED	Reregistration Eligibility Decision
RDDR	Regional Dose Deposition Ratio
SAR	structure activity relationship
SF	safety factor
SSTS	Section Seven Tracking System
TEP	typical end-use product
TGAI	technical grade active ingredient
TMDL	total maximum daily loads
UF	uncertainty factor
UV/VIS	ultraviolet/visible light absorption
% w/w	percent weight per weight.
WP	wettable powder
WWTPs	wastewater treatment plants

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1 Introduction

This document is the United States Environmental Protection Agency's (USEPA, EPA or "the Agency") Final Work Plan (FWP) for 1,2-Benzisothiazol-3(2H)-one, 2-butyl, herein referred to as BBIT. The FWP document explains what EPA's Office of Pesticide Programs (OPP) knows about BBIT, highlighting anticipated data and assessment needs, identifying the types of information that would be especially useful to the Agency in conducting the review, and providing an anticipated timeline for completing BBIT's review.

The registration review process was designed to include a public participation component to solicit input from interested stakeholders. The Agency intends, by sharing this information in the docket, to inform the public of what it knows about BBIT and what types of new data or other information would be helpful for the Agency to receive as it moves toward a decision on BBIT.

1.1 Statutory and Regulatory Authority

The Food Quality Protection Act (FQPA) of 1996 mandated a registration review program. All pesticides distributed or sold in the United States generally must be registered by the USEPA based on scientific data showing that they will not cause unreasonable risks to human health or the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects to human health or the environment. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. Information on this program is provided at http://www2.epa.gov/pesticide-reevaluation.

The Agency is implementing the registration review program pursuant to Section 3(g) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The regulations governing registration review begin at 40 CFR 155.40. The Agency will consider benefits information and data as required by FIFRA. The public phase of registration review begins when the initial docket is opened for each case. The docket is the Agency's opportunity to state what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision.

1.2 Updates to the Workplan

Since the publication of the Preliminary Work Plan (PWP), the Agency has made the following updates:

- Updated Table 1, "Anticipated Risk Assessments for Registration Review". No cumulative evaluation is necessary for BBIT as stated in Section 3.4.2. Added a footnote to clarify the occupational handler's date of most recent assessment.
- Updated the timeline in Table 2, "Anticipated Registration Review Schedule".

- Updated Table 6, "Studies Anticipated as Needed for the Registration Review of BBIT". All use sites trigger the anticipated data needs for the ecological and drinking water exposure scenarios.
- Deleted the "Guidance for Commenters" Section.
- Updated Section 7, "Next Steps".
- Updated spelling and grammatical errors.

No public comments were received on the initial docket. No modifications were made to the anticipated data needs and there is no change to the registration review schedule of BBIT. This document makes final the work plan for the BBIT registration review process.

1.3 Case Overview

The docket for BBIT (case 5017) has been established at http://www.regulations.gov in docket number EPA-HQ-OPP-2015-0736. Documents associated with this registration review can be viewed in this docket. Tables 1 and 2 below summarize the issues relevant to this registration review case and the anticipated registration review schedule.

Table 1 –Anticipated Risk Assessments for Registration Review

Risk Assessment	Assessment Necessary to Support Registration Review	Date of Most Recent Assessment	Type of Assessment Required (New/Updated)	Data Anticipated as Needed (See Table 6 for details)
Dietary (food)	No	N/A	None	N/A
Dietary (drinking water)	Yes	N/A	New	WWTP biodegradation simulation studies Aerobic aquatic metabolism
Occupational Handler	Yes	6/8/2009*	Updated	Indoor Exposure – Inhalation Indoor Exposure – Dermal
Residential Handler	Yes	6/8/2009	Updated	Indoor Exposure – Inhalation Indoor Exposure – Dermal
Residential Post Application - Incidental Oral and Dermal	Yes	6/8/2009	Updated	Indoor Surface Residues
Aggregate	Yes	None	New	None
Cumulative	No	None	None	None
Tolerance Review	No	N/A	None	N/A
Ecological	Yes	6/10/2009 (eco) 6/2/2009 (fate)	New	WWTP biodegradation simulation studies Aerobic aquatic metabolism Aquatic plants and animals

N/A = Not applicable
*** This date reflects the most recent assessments completed for the uses listed in Tables 8, 9 and 10. As stated in Section 3.3, the occupational exposures for machinists using BBIT treated metalworking fluids was evaluated in 2015 (US EPA, 2015) using the revised PODs and does not need to be reevaluated.**

BBIT is used primarily as an antimicrobial, microbiocide/microbiostat, and fungicide/fungistat in metalworking fluids, plastics, polymers, and construction materials. The BBIT case has one pesticidal active ingredient identified under PC Code 098951. The Agency has created the following estimated timeline in Table 2 for the completion of BBIT registration review.

Table 2 – Anticipated Registration Review Schedule

Anticipated Activity	Target Date*	Completion Date
Phase 1: Opening the Docket		
Open Docket and 60-Day Comment Period for Preliminary Work Plan	2016-03	2016-04-11
Close Public Comment Period	2016-05	2016-06-10
Phase 2: Case Development		
Issue Final Work Plan	2016-09	2016-09
Issue Data Call-In (DCI)	2017-09	
Receive Data to be Considered in Risk Assessment	2019-09	
Open 30-Day Public Comment Period for Preliminary Risk Assessment(s)	2021-03	
Close Public Comment Period	2021-04	
Phase 3: Registration Review Decision and Implementation		
Open 60-Day Public Comment Period for Proposed Decision	2021-09	
Close Public Comment Period	2021-11	
Issue Final Decision	2022-03	
Begin Post-Decision Follow-up	2022	
Total (years)	6	

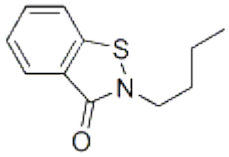
*The anticipated schedule will be revised as necessary (*e.g.*, need arising under the Endocrine Disruptor Screening Program with respect to the active ingredients in this case).

1.4 Chemical Identification and Properties

Table 3 contains the chemical identification of BBIT (PC Code 098951) which belongs to the isothiazolinone chemical family. There are several pesticidal active ingredients in this chemical family which have similar pesticidal, toxicological and environmental behavior characteristics in common. In the absence of existing data, EPA is choosing to bridge data between compounds in this class. Table 4 compares some of the chemical and physical properties of BBIT and the active ingredient, 1,2-Benzisothiazol-3(2H)-one (BIT, PC Code 098901). Additional chemical and physical properties of the BIT transformation products may be seen in Appendix E.

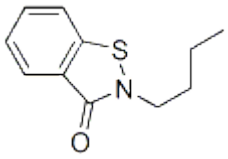
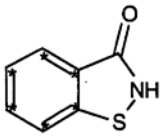
Table 3 – Chemical Identification of BBIT

Chemical Name	N-butyl-1,2-benzisothiazolin-3-one (BBIT)
Chemical Classification	Isothiazolinone
PC Code	098951
CAS Number	4299-07-4

Smiles code	CCCCN1C(=O)C2=CC=CC=C2S1
Molecular Formula	$C_{11}H_{13}NOS$
Molecular Weight (grams/mole)	207.29
Molecular Structure	

The physical and chemical property information from BBIT is presented in Table 4. Some of these data are based on EPI-Suite 4.11 and some are based on the studies for the active ingredient BIT, which has the same ring structure without the four-carbon chain.

Table 4 – Physical-Chemical and Environmental Fate Properties for BBIT and BIT

Guideline No./ Study Type	BBIT	BIT
Structure		
Water Solubility(mg/L)	418 at 25 °C	1,380 mg/L at 24 °C
830.7050 UV visible sorption	Absorption from 290-350 nm (BIT)	Absorption from 290-350 nm (BIT)
830.7370 Dissociation constant (pKa)	Acid dissociation constant 9.12 x 10^{-8} moles/L (PAI) pKa 7.04 at 25 °C (BIT)	Acid dissociation constant 9.12 x 10^{-8} moles/L (PAI) pKa 7.04 at 25 °C (BIT)
830.7550 Partition coefficient (log Kow)	2.32	1.4
830.7950 Vapor pressure (mm Hg)	9.9 x 10^{-6}	1.14 x 10^{-6}
Henry's Law Constant (calculated) Atm m^3 mol^{-1}	6.5 x 10^{-9}	1.64 x 10^{-10}

atm-m^3/mol = atmosphere cubic meter per mole; °C = degrees Celsius; mg/L = milligrams per liter; mmHg = millimeters of mercury

1.5 Use/Usage Description

1.5.1 Registrations

There are five EPA-registered active products that contain BBIT as an active ingredient (a.i.). One of these products is a technical product (EPA Reg. No. 1258-1267) and the other four

products are end-use products,[1] of which one is a ready-to-use and three are soluble concentrates. The percent a.i. for BBIT ranges from 4.75 to 99.2 percent.

1.5.2 Summary of Registered Uses

Table 5 presents a summary of the registered uses of BBIT that will be assessed in this registration review. BBIT can only be applied to metalworking fluids in closed metalworking and delivery systems. In cross linked polyurethane, BBIT products are added to the polyol at a concentration that will yield the desired use level in the final product after reaction with the isocyanate component; however, BBIT products may also be incorporated at an injection port of a reaction injection molding machine. In addition to melt processed polymers (PVC, thermoplastic polyurethane, synthetic elastomers and thermoplastic acrylics, etc.), BBIT products may be metered into the melt to yield the desired end use concentration. For thermoplastic polyurethane, concentrated granules may be produced by absorbing BBIT products through shear mixing. BBIT products may be added to silicone oil for silicone sealants before processing, or to the manufacturing vessel before packing off into containers for supply chain distribution.

Table 5 – BBIT Registered Uses

Use	Application Method	Application Rate
Material Preservative		
Construction Materials (latex emulsions, mineral or pigment slurries)	Open Pour	500 ppm
Construction Materials (paints, coatings, adhesives, caulks, spackle)	Open Pour	1,150 ppm
Metalworking Fluids (initial dose)	Closed System	200 ppm
Metalworking Fluids (maintenance dose)	Closed System	30 ppm
Paper (insulation and wall board facing)	Open Pour	1,150 ppm
Paper (stationary and non-food contact packaging)	Open Pour	1,150 ppm
Plastics (PVC, polyurethane foam and latex rubber)[A, B]	Open Pour	5,000 ppm
Plastics (silicones, polyesters, polyolefins, elastomers)[A,B]	Open Pour	10,000 ppm
A. Plastic items include coated fabrics, pet toys, shower curtains, foam seat cushions and mattress padding, floor coverings, tarps, synthetic leather for sneakers, swimming pool liners and marine hose and sleeving. B. Labels state: “Do not use to treat food/feed or drinking water contact items or children’s toys.”		

1.5.3 Usage Information

Production volume data in the Agency’s Section Seven Tracking System (SSTS) for the years 2003 through 2013 indicate that no more than 250,000 kilograms of BBIT are sold per year in the United States. Data for the years 2014 and 2015 were not used in this estimate since data collection is still in progress.

[1] EPA Reg. Nos. 1258-1249, 1258-1251, 1258-1285, and 1258-1286.

1.6 Regulatory History

The first product containing BBIT chemical as an active ingredient was registered in the United States in April of 2003. This registration was supported by a human health risk assessment (US EPA, 2003) that evaluated occupational and residential exposures involved in treating plastic materials. Additional assessments were done to evaluate proposed uses in metalworking fluids (US EPA, 2004), and construction materials and coatings including wood coatings and stains (US EPA, 2009). The most recent human health risk assessment for BBIT (US EPA, 2015) evaluated a proposed label amendment for the metalworking fluid use to eliminate the requirement for the use only in enclosed machines with local exhaust ventilation. Due to inhalation risk concerns, the closed metalworking system requirement remains in place. The Agency has not conducted an environmental fate or ecological effects assessment for the currently-registered uses.

A Reregistration Eligibility Decision (RED) was not completed for BBIT because it was registered after November 1, 1984.

1.6.1 Tolerance Information

EPA has not established any tolerance or exemptions from the requirement of tolerances in raw agricultural commodities or processed food and feed products for BBIT under the Federal Food, Drug and Cosmetic Act (FFDCA) Section 408. BBIT has not been cleared as a food additive by the US Food and Drug Administration (US FDA) under FFDCA Section 409.

1.7 Incidents

1.7.1 Human Health

There are no incidents reported for BBIT in the OPP Incident Database System based on a search conducted on February 4, 2016.

1.7.2 Ecological

No ecological incidents in the Incident Data System as of November 24, 2015.

2 Anticipated Data Needs

Table 6 presents a summary of the data anticipated as being needed to support this registration review.

Table 6 – Studies Anticipated as Needed for the Registration Review of BBIT

GLN	Study Name	Test Substance	Time Frame[1]	Risk Assessment(s) Data Will Support	Use Site(s) Triggering Anticipated Data Requirement	Applicable Exposure Scenario
835.3110, 835.3220, 835.3240, 835.3280[2,3]	WWTP biodegradation studies	TGAI (BBIT or BIT)	12	Aquatic exposure	All	Ecological Drinking Water
835.4300[3]	Aerobic aquatic metabolism	TGAI (BBIT or BIT)	24	Aquatic exposure	All	Ecological Drinking Water
850.4500[4]	Algal toxicity	TGAI	12	Aquatic plants	All	Ecological
850.4550[4]	Cyanobacteria	TGAI	12	Aquatic plants	All	Ecological
850.1400	Fish, Early Life - Stage	Degradates[5]	24	Aquatic animals	All	Ecological
850.1300	Aquatic Invertebrate Life Cycle	Degradates[5]	24	Aquatic animals	All	Ecological
875.1200[6]	Dermal Exposure - Indoor	TEP	24	Human Health	Paints and Coatings	Open Pour Liquids, Airless Spray and Brush/Roller Paint Application
875.1400[6]	Inhalation Exposure - Indoor	TEP	24	Human Health	Paints and Coatings	Open Pour Liquids Airless Spray and Brush/Roller Paint Application
875.2300[6]	Indoor Surface Residues	TEP	24	Human Health	Plastics (Vinyl Flooring) Pet Toys Foam Based Mattress Pads	Dermal and Hand to Mouth Exposure

1 The timeframe is measured in months from DCI Receipt.

2 An ASRI for BIT provided a value of 30 mg/L (>20 mg/L). Therefore, the registrant must conduct either: (i) Ready Biodegradability or (ii) a) Biodegradation in Activated Sludge or b) Simulation Test - Aerobic Sewage Treatment: A. Activated Sludge Units or c) the Porous Pot Test. If the Ready Biodegradability study is conducted and passes, then no further testing is required. If, however, the antimicrobial fails the Ready Biodegradability study, then the a) Biodegradation in Activated Sludge or b) Simulation Test - Aerobic Sewage Treatment: A. Activated Sludge Units, or c) the Porous Pot study is required.

3 Biodegradation or Aerobic aquatic metabolism data may be generated for either BIT or BBIT; bridging from BIT is appropriate based on the similarity in chemical structure.

4 Green algae (*Selenastrum capricornutum*) data are required for this use pattern. If the EC_{50} of BBIT is less than 1.0 mg/L, studies are also required on three additional species (*Anabaena flos-aquae*, *Navicula pelliculosa*, and *Skeletonema costatum*). The Public Draft OPPTS 850.5400 Algal Toxicity guideline was split into two separate guidelines and renumbered with the cyanobacteria species separated into OCSPP 850.4550 and the other three species under OCSPP 850.4500.

5 Based on identification of any significant degradates from the Aerobic aquatic metabolism study (835.4300). If major degradates persist for more than one week in water, chronic testing for freshwater fish and invertebrates is needed.

6 A protocol must be approved by the Agency prior to the initiation of the study.

3 Human Health Risk Assessment

The Agency anticipates the need to conduct a human health risk assessment for BBIT. The Agency expects to require additional data for use in conducting the registration review.

For the purpose of risk assessment of isothiazolinone chemicals group, the Agency determined that chemical-specific data will be used when available. If there are no chemical-specific data, the most conservative stud(ies) of the group should be used for deriving the endpoint(s). Some toxicity studies are not available for BBIT; therefore, data were bridged from other isothiazolinone chemicals for establishing the appropriate endpoints. Although no additional toxicity studies are required for BBIT presently, the Agency recommends that the registrant submit any relevant chemical-specific information, including valid literature studies, to refine the risk assessment for BBIT, particularly for chronic dietary, dermal, and inhalation endpoints.

Additionally, the Agency anticipates to require additional exposure studies, based on the currently registered uses, for the registration review of BBIT. A detailed description of the available toxicity studies is provided in Appendix A.

3.1 Toxicological Endpoints

The Agency recently revised the existing toxicological endpoints for the entire isothiazolinone chemicals group, to which BBIT belongs. All available information, including existing toxicology studies for the isothiazolinone chemicals as well as valid scientific literature, were considered in establishing the current toxicology endpoints. As a result, the Agency does not anticipate the need to revise the current toxicology endpoints for BBIT, as part of the registration review. The current toxicological endpoints for BBIT are shown in Table 7 below.

When revising the existing toxicological endpoints for the isothiazolinone chemicals group, the Agency concluded, when appropriate, that the default 10x uncertainty factors (UF) be reduced to 3x, i.e., remove the toxicokinetic component of the UF (3x for inter-species extrapolation and 3x for intra-species variation) for short-term (ST) and intermedium-term (IT) risk assessments for all routes of exposure, based upon (1) observed effects being portal of entry, local irritation-like effects irrespective of route of exposure, (2) the lack of systemic toxicities, and (3) no metabolic activation or degradation to a toxic moiety. The Agency also recommended that additional uncertainty factors may be used to account for (1) database uncertainty, (2) adjustment of exposure durations, and/or (3) use of a lowest-observed-adverse-effect-level (LOAEL) for the point of departure (POD). This decision applies to all of the isothiazolinone chemicals.

No chronic/cancer studies are available for BBIT; therefore, the CMIT/MIT chronic/cancer study with a no-observed-adverse-effect-level (NOAEL) of 2.0 mg/kg/day was selected for chronic dietary exposure. The UF is 10x (UF_A = 3x for interspecies extrapolation and UF_H = 3x for intraspecies variations).

There is no dermal study for BBIT. For dermal exposure scenarios (all durations), the CMIT/MIT 90-day dermal study with a LOAEL of 0.75 mg/kg/day was selected as it is a route-specific study with the most conservative endpoint. The UF for ST and IT dermal exposure

scenarios is 30x (UF_A = 3x for interspecies extrapolation, UF_H = 3x for intraspecies variations, and $UF_{LOAEL \rightarrow NOAEL}$ = 3x for LOAEL to NOAEL extrapolation). The UF for long-term (LT) dermal exposure scenarios is 100x (UF_A = 3x for interspecies extrapolation, UF_H = 3x for intraspecies variations, $UF_{LOAEL \rightarrow NOAEL}$ = 3x for LOAEL to NOAEL extrapolation, and UF_{DB} = 3x for using a 90-day study for long-term exposure scenario).

There is no inhalation study for BBIT. For inhalation exposure scenarios (all durations), the DCOIT 90-day inhalation study with a no-observed-adverse-effect-concentration (NOAEC) of 0.02 mg/m^3 was selected as it is a route-specific study with the most conservative endpoint. The UF for ST and IT inhalation exposure scenarios is 10x (UF_A = 3x for interspecies extrapolation and UF_H = 3x for intraspecies variations). The UF for long-term (LT) inhalation exposure scenarios is 30x (UF_A = 3x for interspecies extrapolation, UF_H = 3x for intraspecies variations, and UF_{DB} = 3x for using a 90-day study for long-term exposure scenario).

Table 7 –Toxicological Endpoints for BBIT

Exposure Scenario	Dose or Concentration Used in Risk Assessment	Target Margin of Exposure (MOE), Uncertainty Factor (UF)	Study and Toxicological Effects
Acute Dietary (females 13-49)	No appropriate endpoint identified from the BBIT database.		
Acute Dietary (general population including infants and children)	NOAEL = 2000 mg/kg/day	**UF =100x** (UF_A = 3x for interspecies extrapolation, UF_H = 3x for intraspecies variations, and $UF_{LOAEL \rightarrow NOAEL}$ = 10x for LOAEL to NOAEL extrapolation)	BBIT Acute Oral Study (MRID 44364915) LOAEL = 2000 mg/kg/day, based on clinical signs of toxicity observed on Day 1 (piloerection, sides pinched in, upward curvature of spine, labored breathing, gasping, signs of salivation, breathing irregular, ↑ breathing depth & rate, prostrate, and tip toe gait) death of one female rat on Day 2.
Chronic Dietary (General Population)	NOAEL = 2.0 mg/kg/day	**UF =10x** (UF_A = 3x for interspecies extrapolation and UF_H = 3x for intraspecies variations)	CMIT/MIT Chronic/Cancer (Drinking Water) Study – Rat[1] (MRID 43140701) LOAEL = 6.6/9.8 mg/kg/day, based on increased incidence of hyperplasia/ hyperkeratosis of the squamous mucosa of the forestomach in female rats (17/80 rats *vs* 5/80 and 5/80 in water and salt controls, respectively), necrosis of the granular mucosa in female rats (11/80 rats *vs* 3/80 in water control), and increased incidence of edema/inflammation of the submucosa of the glandular stomach in females (9/80 *vs* 1/80 and 3/80 in water and salt controls, respectively).

Exposure Scenario	Dose or Concentration Used in Risk Assessment	Target Margin of Exposure (MOE), Uncertainty Factor (UF)	Study and Toxicological Effects
Incidental Oral (short- [1-30 days]/ intermediate-term [1-6 months])	$NOAEL_{offspring\ systemic}$= 49 mg/kg/day (600 ppm)	**UF =100x** (UF_A = 10x for interspecies extrapolation and UF_H = 10x for intraspecies variations)	BBIT Two-generation Reproduction (Dietary) – Rat (MRID 48261201) **$LOAEL_{parental\ systemic}$=1700 ppm (141/157 mkd ♂/♀)**, based on ↓ body weights (pre-mating slightly but sig. in ♂ [↓4% WK1 and ↓5% WK 3]); pre-mating body wt gains (♂/♀: ↓18%/29% during WK 0-1; overall pre-mating [WK 0-10] wt gains ↓10% in ♀ but not sig. in ♂) and food consumption (♂: absolute ↓4-11% during WK 0-1, 2-3, & 3-4; relative ↓9%) and food efficiency (↓10%. ♀: absolute ↓5% each during WK 0-1 & WK 1-2 and relative ↓7% during WK 0-1). **$NOAEL_{offspring\ systemic}$ = 600 ppm (49/56 mkd ♂/♀)** **$LOAEL_{offspring\ systemic}$ = 1700 ppm (141/157 mkd ♂/♀)**, based on ↓ body weights (♂/♀: pre-mating ↓6-17%/7-17% [WK 18-28]), body weight gains (♂: ↓8% WK 18-19), and spleen weight (absolute/relative [to body] ↓9-19% on PND 21 in F2 pups ♂ & ♀] only). **$NOAEL_{repro}$ = 1700 ppm (141/157 mkd ♂/♀)**
Dermal (all durations)	LOAEL = 0.75 mg/kg/day (skin loading dose[2] =1.2 µg/cm^2)	Short- and intermedium-term: **UF =30x** (UF_A = 3x for interspecies extrapolation, UF_H = 3x for intraspecies variations, and $UF_{LOAEL \rightarrow NOAEL}$ = 3x for LOAEL to NOAEL extrapolation) Long-term: **UF =100x** (UF_A = 3x for interspecies extrapolation, UF_H = 3x for intraspecies variations, $UF_{LOAEL \rightarrow NOAEL}$ = 3x for LOAEL to NOAEL extrapolation, and UF_{DB} = 3x for using a 90-day study for long-term exposure scenario)	CMIT/MIT 90-Day Dermal – Rat[3] (MRID 43462005) $LOAEL_{dermal}$ = 0.75 mg/kg/day, based on (i) mild erythema in females at 0.75 mg/kg/day and greater beginning on Day 22 of the study; 0.75 mkd (3/10), 3.75 mkd (6/10), 18.75 (10/10) and desquamation and eschar formation and (ii) similar skin effects in males noted in mid- and high-dose groups; 0.75 mkd (0/10), 3.75 mkd (2/10), and 18.75 mkd (10/10).

Exposure Scenario	Dose or Concentration Used in Risk Assessment	Target Margin of Exposure (MOE), Uncertainty Factor (UF)	Study and Toxicological Effects
Inhalation (all durations)	NOAEC = 0.02 mg/m^3 ($HEC_{8\text{-hour}}$ = 0.0045 mg/m^3)[4]	Short- and intermedium-term: **UF =10x** (UF_A = 3x for interspecies extrapolation and UF_H = 3x for intraspecies variations) Long-term: **UF =30x** (UF_A = 3x for interspecies extrapolation, UF_H = 3x for intraspecies variations, and UF_{DB} = 3x for using a 90-day study for long-term exposure scenario)	DCOIT 90-day Inhalation Toxicity Study – Rat[5] (MRID 43487501) LOAEC = 0.63 mg/m^3, based on hyperplasia of the larynx (13/16 animals vs. 1/15 in control), chronic inflammation of the larynx (5/16 vs. 0/15 in control), squamous metaplasia of the larynx (14/16 vs. 0/15 in control), and transitional respiratory epithelium hyperplasia (nose level 1: 4/16 vs 0/15 in control) for male rats. In females, chronic inflammation of the larynx (9/16 vs 0/15 in control) and squamous metaplasia (16/16 vs. 0/15 in control) were also observed, as well as goblet cell hyperplasia (7/16 vs. 0/15 in control) and transitional respiratory epithelium hyperplasia (3/16 vs 0/16 in control). Increased incidence of histopathological alterations of the nose, larynx, and lung

NOAEL/C = no observed adverse effect level/concentration, LOAEL/C = lowest observed adverse effect level/concentration

[1] No chronic/cancer studies are available for BBIT; therefore, data were bridged from a chronic/cancer study in drinking water for CMIT/MIT.

[2] Skin Loading (µg/cm^2) = (LOAEL 0.75 mg of 13.9% CMIT/MIT/kg/day x 1000 µg/mg unit conversion x 13.9%/100 ai adjustment x 0.4 kg BW rat)/35 cm^2 applied dose = 1.2 µg/cm^2

[3] No 90-day dermal toxicity studies are available for BBIT; therefore, data were bridged from a 90-day dermal study for CMIT/MIT.

[4] 8-hour Human Equivalent Concentration ($HEC_{8\text{ hour}}$) = NOAEC x (6 hours animal tox study/8 hours human exposure) x RDDR, where the RDDR is 0.30 for extrathoracic (ET) effects (MMAD = 1.4 µm, GSD = 4.6 and BWrat = 420 grams). Rat BW is the average for the 0.63 mg/m^3 treatment group at Week 13.

[5] No 90-day inhalation toxicity studies are available for BBIT; therefore, data were bridged from a 90-day inhalation study for DCOIT.

3.2 Dietary Exposure

A dietary (food) exposure assessment is not required for BBIT at this time. The Agency will examine the need for a drinking water assessment during the risk assessment stage of this Registration Review.

3.2.1 Food

BBIT uses are not expected to result in direct or indirect dietary (food) exposure since all FIFRA-registered BBIT labels specify the product is not intended for use in/on surfaces that may contact food. Therefore, the registered uses of BBIT are not expected to result in direct or indirect dietary (food) exposure and a dietary (food) exposure assessment is not anticipated to be needed.

3.2.2 Drinking Water

A drinking water assessment has not been conducted for BBIT in the past. However, for the metalworking fluid and paper production uses, the Agency cannot rule out the potential for BBIT to enter surface water and to subsequently be present in drinking water. Since drinking water risk is a function of many unknown factors including (1) the residues of concern in drinking water, (2) the magnitude of these potential residues of concern, (3) the persistence of BBIT in water, and (4) if residues of BBIT are likely to pass through a wastewater treatment plant (WWTP), the Agency anticipates needing environmental fate data listed in Section 4 of this FWP. These data from either BIT or BBIT will be used to determine whether, and to what extent, residues of BBIT will pass through a WWTP and persist in surface water. Upon receipt and review, these data and other available sources of information will be used during the risk assessment stage of this Registration Review to determine the potential for discharged or leached residues of BBIT to result in human dietary exposure via drinking water, which may trigger a drinking water assessment.

3.3 Occupational and Residential Exposures

The occupational and residential exposures that were evaluated in the previous risk assessments (US EPA, 2003, US EPA, 2004, US EPA, 2009) will need to be reevaluated to account for the toxicology PODs that were revised in 2015 and new exposure and surface residue studies that are anticipated to be needed. The occupational exposures for machinists using BBIT treated metalworking fluids was evaluated in 2015 (US EPA, 2015) using the revised PODs and does not need to be reevaluated.

3.3.1 Occupational Handler Exposure

The occupational handler dermal and inhalation exposures were previously assessed using a POD of 30 mg/kg/day that was based on an oral toxicity study. Dermal exposures will need to be reassessed using the revised POD of 1.2 ug/cm^2 that is based on a dermal toxicity study, and inhalation exposures will need to be reassessed using the revised POD of 0.0045 mg/m^3 that is based on an inhalation toxicity study.

In addition, Series 875 dermal and inhalation exposure studies will be needed to replace the data from the Pesticide Handlers Exposure Database (PHED) and the Chemical Manufacturer Association (CMA) study that were used in the previous assessments because these data do not have adequate quality control information (such as field and laboratory recovery samples, method validation samples) and number of replicates (i.e., number of times a worker is monitored for a specific activity). EPA presented the need for additional handler exposure data to the January 2007 Science Advisory Panel (SAP) as well as to the April 2007 Human Studies Review Board (HSRB) and both groups agreed that additional data are warranted.

The occupational handler exposure scenarios that will need to be evaluated are listed in Table 8.

Table 8 – Occupational Handler Exposure Scenarios for BBIT

Exposure Scenario	Exposure Route(s)	Duration
Open Pour Liquids During Material Preservation	Dermal Inhalation	Short, Intermediate, and Long Term
Airless Sprayer and Brush/Roller Application of Preserved Paints	Dermal Inhalation	Short and Intermediate Term

3.3.2 Residential Handler Exposures

The residential handler dermal and inhalation exposures were also previously assessed using the POD of 30 mg/kg/day and will need to be reassessed using the revised PODs of 1.2 ug/cm^2 for dermal exposure and 0.0045 mg/m^3 for inhalation exposure. In addition, dermal and inhalation exposure data will be needed to replace the data that were used in the previous assessments as discussed above for occupational handlers. The residential handler exposure scenarios that will need to be evaluated are listed in Table 9.

Table 9 – Residential Handler Exposure Scenarios for BBIT

Exposure Scenario	Exposure Route(s)	Duration
Airless Sprayer and Brush/Roller Application of Preserved Paints	Dermal Inhalation	Short and Intermediate Term

3.3.3 Residential Post-Application Exposures

The residential post application dermal and incidental oral exposures were previously assessed using the POD of 30 mg/kg/day and will need to be reassessed using the revised PODs of 1.2 ug/cm^2 for dermal exposure and 49 mg/kg/day for incidental oral exposure. In addition, 875.2300 surface residue studies are needed to replace those studies used in the previous assessment because the previously used studies were experimental in nature and did not include the quality control data that is normally included in guideline studies. The residential post application exposure scenarios that will need to be evaluated are listed in Table 10.

Table 10 – Residential Post-Application Exposure Scenarios for BBIT

Exposure Scenario	Exposed Population	Exposure Route(s)	Duration
Playing on Treated Vinyl Flooring	Children	Dermal Incidental Oral	Short and Intermediate Term
Playing with Treated Pet Toys	Children	Dermal Incidental Oral	Short and Intermediate Term
Sleeping on Foam Based Mattress Pads	Adults and Children	Dermal	Short and Intermediate Term

3.4 Aggregate and Cumulative Exposure

3.4.1 Aggregate Exposures

EPA plans to conduct an aggregate assessment for BBIT because this assessment was not conducted previously. This assessment will include dietary (drinking water) exposures and residential incidental oral exposures. It is anticipated that dermal and inhalation exposures will not be aggregated with the dietary and incidental oral exposures because the effects of dermal and inhalation exposures observed in the dermal and inhalation toxicology studies are irritation effects which are not similar to the systemic effects seen in the oral studies.

3.4.2 Cumulative Exposures

In 2015, EPA's Office of Pesticide Programs released a guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups[2] and conducting cumulative risk assessments.[3] The Agency has utilized this framework for BBIT and determined that although BBIT shares some chemical and/or toxicological characteristics (e.g., chemical structure or apical endpoint) with other pesticides, the toxicological database does not support a testable hypothesis for a common mechanism of action. No further data are required to determine that no common mechanism of toxicity exists for BBIT and other pesticides and no cumulative evaluation is necessary for BBIT.

4 Environmental Risk Assessment

The Agency has not previously conducted and anticipates the need to conduct an ecological risk assessment for BBIT. The Agency expects to require additional data for use in conducting the registration review.

The ecological risk assessment planned during registration review will allow the Agency to determine potential acute and chronic risks to aquatic organisms exposed to BBIT that are transported from treatment sites into the aquatic environment. The risk assessment also will allow the Agency to determine whether each use of the BBIT has 'no effect' or 'may affect' federally listed threatened or endangered species (listed species) or their designated critical habitats. When an assessment concludes that a pesticide's use 'may affect' a listed species or its designated critical habitat, the Agency will consult with the U.S. Fish and Wildlife Service and/or National Marine Fisheries Services (the Services), as appropriate.

[2] Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999)
[3] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

4.1 Environmental Fate Assessment

Hydrolysis data are available for BBIT. For all other fate parameters, since BBIT consists of BIT with the addition of a 4-carbon aliphatic chain and based on the similarity of structures and physical-chemical properties between BIT and BBIT, environmental fate properties of BBIT are expected to be similar to BIT. Consequently, the environmental fate assessment for BBIT is based primarily on data from BIT. Even though the Agency is not requiring BBIT specific data, registrants may opt to submit BBIT specific data in order to refine the environmental fate assessment. A summary of the environmental fate data for BIT and BBIT is presented in Table 11.

There were five significant transformation products identified for BIT and each product had an intact benzene ring. These include:

- Hydroxy-1,2-benzisothiazol-3-one (hydroxylated BIT),
- Saccharin (BIT sulfone), and
- BIT-S-Oxide (BIT sulfoxide)
- 2-sulfobenzamide (Ortho-sulfobenzamide)
- 1,2-benzthiazolin-2-one

Chemical structures of these five products are presented in Appendix B. Of these five transformation products, three had both intact benzene and isothiazolinone rings, including:

- Hydroxy-1,2-benzisothiazol-3-one (hydroxylated BIT),
- Saccharin (BIT sulfone), and
- BIT-S-Oxide (BIT sulfoxide).

BBIT is water soluble and is not likely to volatilize from water. BBIT and BIT are both stable to hydrolysis (MRIDS 44364926 and 47329401).

BIT transforms rapidly by photodegradation in water with half-lives of 9 hours at pH 5 and 0.7 hours at pH 7 and 9. The photodegradation half-life was about 1 day for the total of BIT and the two transformation products with intact benzene ring and isothiazolinone rings, hydroxy BIT and saccharin (MRID 47329402).

In the aerobic soil metabolism study, the half-life of BIT was reported to be less than one day (MRID 41199102), but there is uncertainty about the persistence and occurrence of the transformation products, 2-sulfobenzamide, BIT sulfoxide, and BIT sulfone (MRID 41199103).

BIT was moderately mobile based on Kads values of 1.3-12.2 L/kg and Koc values of 254-728 L/kg. Sorption was related to clay and organic content (MRID 41687102).

Table 11 – Environmental Fate and Transport Properties of BBIT and BIT

Property (Guideline number)	**Value**	**Reference (MRID unless specified)** **Comments**
Hydrolysis (161-1, 835.2120)	Stable at 5, 7, and 9	44364926 (BBIT) 47329401 (BIT)
Photodegradation in water (161-2, 835.2210)	Stable in dark controls 9 hours (pH 5), 0.7 hours (pH 7 and 9)	47329402 (BIT) Data for BBIT not required Major transformation products Ortho-sulfobenzamide 1,2-benzthiazolin-2-one hydroxy-1,2-benzisothiazolin-3-one (hydroxy BIT) Saccharin
Aerobic soil metabolism (162-1, 835.4100)	Half-life of <1 day for BIT (observed) 90 % dissipation of BIT by 7-28 days and 98-99 % dissipation by 60-180 days	41199102 and 41199103 (BIT) Data for BBIT not required Ortho-sulfobenzamide and BIT-S-oxide were significant transformation products
Leaching-Adsorption-Desorption (163-1, 835.1230)	Kads (Kocs) in L/Kg 2.5 (486) 1.3 (254) 12.2 (728) 2.5 (389)	41687102 (BIT) BIT data is bridgeable to BBIT Loamy sand Loam Silty clay loam Silt loam
Anaerobic aquatic metabolism (162-4, 835.4400	Not required (BIT and BBIT)	Waived for BIT because of lack of sorption Also waived for BBIT because of structural similarity between BIT and BBIT
Aerobic aquatic metabolism (162-3, 835.4300)	Required (BIT or BBIT)	Data on aerobic aquatic metabolism were required in December 2014 Final Work Plan for BIT BIT data is bridgeable to BBIT
Activated Sludge Sorption Isotherm (ASSI)	Not required (BIT and BBIT)	Not required because measured log Kow values for BIT (1.4) and BBIT (2.32) are less than 3 (Table E3)
Activated Sludge Respiration Inhibition (ASRI, 850.6800, OECD 209)	For BIT EC_{50} = 30 mg/L EC_{20} = 11.5 mg/L EC_{80} = 79 mg/L. NOEC = 1 (one) mg/L.	47759819 (BIT) BIT data is bridgeable to BBIT
Biodegradation in wastewater treatment plants (835.3110, 835.3220, 835.3240, 835.3280)	Required (BIT or BBIT)	BIT data is bridgeable to BBIT

4.1.1 Water and Sediment

BBIT is water soluble and is not likely to volatilize from water. BBIT and BIT are both stable to hydrolysis with extrapolated half-lives of >1 year (MRIDs 44364926 and 47329401), but BIT degrades rapidly by photodegradation in water with half-lives of 9 hours at pH 5 and 0.7 hours at pH 7 and 9. The photodegradation half-life in water of the sum of BIT and two transformation products with intact benzene and isothioazolone rings (hydroxy BIT and saccharin) was about 1 day (MRID 47329402).

4.1.2 Soil

In the aerobic soil metabolism study, the half-life of BIT was reported to be less than one day (MRID 41199102). However, there is uncertainty about the persistence and occurrence of the transformation products since the percent formation of 2-sulfobenzamide, BIT sulfoxide, and BIT sulfone, was only quantified at day 7 and day 28 of a 180-day study (MRID 41199103).

BIT was moderately mobile based on Kads values of 1.3-12.2 L/kg and Koc values of 254-728 L/kg. Sorption was related to clay and organic content (MRID 41687102).

4.1.1 Air

Based on the vapor pressure and Henry's Law constants for BBIT and BIT in Table 4 and for the BIT transformation products in Table 5, movement from soil or water to air is not expected to be a significant transport process.

4.2 Water Quality

BBIT is not identified as a cause of impairment for any water bodies listed as impaired under section 303(d) of the Clean Water Act.[4] In addition, no Total Maximum Daily Loads (TMDL) have been developed for BBIT.[5] More information on impaired water bodies and TMDLs can be found at the Agency's website.[6] **The Agency invites submission of water quality data for this pesticide.** To the extent possible, data should conform to the quality standards in Appendix A of the *OPP Standard Operating Procedure: Inclusion of Impaired Water Body and Other Water Quality Data in OPP's Registration Review Risk Assessment and Management Process*[7] in order to ensure they can be used quantitatively or qualitatively in pesticide risk assessments.

4.3 Conceptual Models for Environmental Exposure Pathways

Based on the summary of registered uses of BBIT presented in Table 5, physical/chemical properties of BBIT and BIT in in Table 4, and environmental fate data presented in Table 11, the

[4] http://iaspub.epa.gov/tmdl_waters10/attains_nation_cy.cause_detail_303d?p_cause_group_id=885
[5] http://iaspub.epa.gov/tmdl_waters10/attains_nation.tmdl_pollutant_detail?p_pollutant_group_id=885&p_pollutant_group_name=PESTICIDES
[6] http://iaspub.epa.gov/waters10/attains_nation_cy.control?p_report_type=T
[7] http://www2.epa.gov/pesticide-reevaluation/opp-guidance-submission-state-and-tribal-water-quality-monitoring-data

Agency has created conceptual models for potential routes of environmental exposure which are included in "Conceptual Models for Environmental Exposure Pathways of Antimicrobial Pesticides" (EPA-HQ-OPP-2014-0638-0002), found in the docket at www.regulations.gov, EPA-HQ-OPP-2014-0638. For metalworking fluids, refer to slide 18. For paper production, refer to slide 26. For construction materials, refer to slide 17. For plastics, refer to slide 15. All relevant routes of environmental exposure will be considered in the risk assessment.

4.4 Ecological Effects Assessment

4.4.1 Measures of Effect

Ecological effects data are used as measures of direct and indirect effects to aquatic and terrestrial organisms. Acute and chronic toxicity data from registrant-submitted studies conducted in accordance with the 850 OCSPP Harmonized Test Guidelines are used to evaluate the potential direct and indirect effects to plants and animals. Relevant data from the open literature also may be used if available.

4.4.1.1 Data Submitted for BIT

No data have been submitted for BBIT. Data for BIT are being bridged to BBIT (see section 4.1). All data requirements and available ecotoxicity endpoints from studies submitted by registrants are tabulated in Appendix C. Even though the Agency is not requiring BBIT specific data, registrants may opt to submit BBIT specific data in order to refine the ecological assessment. OPP uses the most sensitive of these endpoints for assessing risk to each terrestrial and aquatic receptor group. The available endpoints selected for the risk assessment are provided in Table 13. A data gap exists for algae and cyanobacteria.

Table 12 – Available Ecological Effects Endpoints

Receptor Group	Test Material	Risk Scenario	Toxicity Endpoint	Reference
Freshwater fish	TGAI	Acute	LC50 = 0.54 mg ai/L	443649-13
		Chronic[1]	NOAEC = 0.28 mg ai/L	477598-15
Freshwater invertebrates	TGAI	Acute	EC50 = 1.5 mg ai/L	455346-01
		Chronic[1]	NOAEC = 0.91 mg ai/L	477598-14
Estuarine/marine fish	TGAI	Acute	LC50 = 12.2 mg ai/L	429450-01
		Chronic	Not required	--
Estuarine/marine invertebrates	TGAI	Acute	EC50 = 0.047 mg ai/L	429524-01
		Chronic	Not required	--
Aquatic plants - Algae and cyanobacteria	TGAI	EC50 NOAEC	Data gap	--

Birds	TGAI	Acute oral	LD50 = 453 mg ai/kg bw	409913-01

1 The Agency has adequate chronic fish and invertebrate data for the parent compound; however, if the aerobic aquatic metabolism study shows degradates that persist, chronic fish and invertebrate data are needed for the degradates.

4.4.1.2 Other Data

The ECOTOX database will be searched during the risk assessment phase and the data will be reviewed following the Agency's policy for reviewing public literature for use in assessing risks from pesticides. Those ecotoxicity values found in the public literature to be more sensitive than those currently in the data and or which satisfy an existing data gap(s) will be used during the risk assessment phase. ECOTOX was created and is maintained by the USEPA, Office of Research and Development, and the National Health and Environmental Effects Research Laboratory's Mid-Continent Ecology Division.

4.5 Exposure Analysis Plan

4.5.1 Screening Level Down-the-Drain Analysis

The Agency will use the General Population and Ecological Exposure from Industrial Releases module of E-FAST (Exposure and Fate Assessment Screening Tool) to estimate the potential for exposure to aquatic organisms located downstream of industrial wastewater treatment plants. These aquatic organisms in streams may receive discharges from in-service uses of products containing BBIT. The results of this module of E-FAST are expressed as number of days of exceedance of concentrations of concern (COC) for aquatic organisms.

5 Endocrine Disruptor Screening Program (EDSP)

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for BBIT, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), BBIT is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to

interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[8] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[9]

6 Optional Label Changes

The Agency invites any label amendments that could be considered to eliminate the anticipated need for EPA to require certain data, reduce the possibility that EPA's planned risk assessments overestimate risk due to reliance on conservative assumptions, and/or improve label clarity.

7 Next Steps

A DCI will be developed requiring generation and submission of the data listed under the "Anticipated Data Needs" Section of this document. The Agency expects to issue the DCI by September of 2017.

[8] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
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US EPA, 2015. 2-Butyl-1, 2-Benzisothiazolin-3 (2H) -One (BBIT): Dermal and Inhalation MOEs for Machinists Using BBIT Treated Metal Working Fluids in Open Systems. D421679, September 10, 2015.

Appendix A Toxicology Profile

Acute Toxicity for Product Labeling

BBIT is Toxicity Category III for both acute oral and acute dermal toxicity. It is Toxicity Category II for inhalation toxicity and Toxicity Category I (Corrosive) for both eye irritation and dermal irritation. BBIT is a dermal sensitizer in female guinea pigs, but not in male guinea pigs.

Table A1– Acute Toxicity Studies for BBIT

Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.1100 purity a.i. (% w/w): 95.5	Acute Oral – Rat	44364915	LD_{50} = 4267 mg/kg (M); 4732 mg/kg (F)	III
870.1200 purity a.i. (% w/w): 93.4	Acute Dermal – Rat	44364916	LD_{50} > 2000 mg/kg	III
870.1300 purity a.i. (% w/w): 45.2	Acute Inhalation – Rat	45083004	LC_{50}>0.733 mg/l (M); 0.197 – 0.733 mg/l (F)	II
870.2400	Primary Eye Irritation	Waived	Corrosive	I
870.2500 purity a.i. (% w/w): 93.4	Primary Skin Irritation – Rabbit	44364917	Corrosive	I
870.2600 purity a.i. (% w/w): 95.5	Dermal Sensitization-Guinea Pig	44364918	Moderate Dermal Sensitizer	Not applicable

Subchronic Toxicity

Adequacy of Database for Subchronic Toxicity: There are two subchronic toxicity studies in the Agency's hazard database to address subchronic oral toxicity, including a subchronic oral toxicity study in rats (MRID 44403001) and a subchronic oral toxicity study in dogs (MRID 48262204). A brief summary of the reviewed studies is provided below.

There are no route-specific subchronic inhalation and dermal toxicity studies for BBIT; these data were bridged from other isothiazolinone chemicals when the toxicology endpoints were revised recently. These studies are not anticipated to be required, at present, for BBIT registration review risk assessment, based on the currently registered uses. However, should new use(s) be added and/or current labels be amended, these studies may be required.

870.3100 90-Day (13-Week) Oral Toxicity – Rat

In a subchronic oral toxicity study (MRID 44403001), 1,2-benziso-thiazolin-3-one, 2-butyl (corrected for 95.5% a.i. purity) was administered to 20 Wistar-derived Sprague Dawley (Alpk:APfSD) rats/sex/dose each in the feed at concentrations of 0, 40, 200, and 2000 ppm for males and females for 90 days. The mean estimated compound intake in males was 0, 3.1, 15.3, or 149.2 mg/kg/day, respectively, and in females was 0, 3.4, 16.6, or 162.4 mg/kg/day, respectively.

Three males died prior to scheduled termination, one control and two 200 ppm males, but the deaths were not considered treatment-related. No clinical signs were observed. There were no treatment-related neurotoxic effects or effects on motor activity. There were no treatment-related effects of toxicological significance on body weight, food consumption, or food efficiency. Transient depression of body weight and food consumption in the 2000 ppm males and females were attributed to decreased feed palatability and produced an overall body weight gain decrease 12%] at 2000 ppm. There were no treatment-related effects on ophthalmologic or hematologic endpoints nor were there gross pathologic or organ weight changes.

Histopathologic changes indicative of irritative effects on the non-glandular stomach were observed in 20% each of the 2000 ppm male and female animals. These consisted of minimal to slight submucosal inflammation with or without epithelial hyperplasia or erosion; one male had a slight ulcer. No animals in either of the lower dose groups or the control groups showed such changes. These changes were considered treatment-related and adverse.

Under the conditions of this study, the subchronic toxicity LOAEL is 2000 ppm (males: 149.2 mg/kg/day; females: 162.4 mg/kg/day) based on submucosal inflammation of the stomach. The NOAEL for male and female rats is 200 ppm (males: 15.3 mg/kg/day; females: 16.6 mg/kg/day).

This subchronic oral toxicity study in rats is classified as **Acceptable/Guideline** and satisfies the [OPPTS: 870.3100 (§82-1)] Subdivision F guideline requirements.

870.3150 90-Day (13-Week) Oral Toxicity – Dog

In a subchronic oral toxicity study (MRID 48262204), N-butyl-1,2-benzisothiazolin-3-one (99.4% a.i.; Lot No. 6180) in the vehicle, corn oil, was administered by gelatin capsule, once daily, to four beagle dogs/sex/dose group at doses of 0, 25, 75 or 250 mg/kg/day for at least 90 days. The high dose was reduced to 200 mg/kg/day beginning on Day 10 due to one female who was sacrificed *in extremis* at 250 mg/kg/day.

No adverse, treatment-related effects were observed on ophthalmoscopic examinations, urinalysis, organ weights or gross or microscopic pathology.

Mortality was observed at high-dose level. One female was sacrificed *in extremis* due to abnormal excreta, dermal atonia, emesis, excessive salivation, hypoactivity and thinness. Treatment-related clinical observations consisted of emesis, diarrhea, soft feces and some mucoid feces in the mid- and high-dose males and females. Treatment-related effects on body weights were observed at high-dose level in both sexes. Males at this dose actually lost weight

($p<0.05$) during Weeks 0-1 and 0-2. Cumulative body weight gains in the males at this dose remained decreased compared to controls throughout the study, and attained statistical significance ($p<0.05$). Overall (Weeks 0-13) body weight gain in high-dose males was decreased compared to controls. As a result of these decreases, body weights were decreased (non-significant) in these males throughout the study. Treatment-related effects in the high-dose females were limited to decreases (non-significant) in body weight during Weeks 1 and 2. All other statistically significant differences from controls in body weight or body weight gain were minor, transient, and/or unrelated to dose. Red blood cell parameters (red cell count, hemoglobin, and hematocrit) were decreased in males and females at both testing intervals (non-significant). This change was not dose-dependent, but the high-dose groups consistently showed the greatest decrease, while higher platelet counts were found in this dose group. A dose-response decrease in serum albumin and total protein concentrations was observed in the high-dose males and females ($p\leq0.01$). Serum albumin concentration was decreased in the low-dose males and total protein concentration was decreased ($p\leq0.05$) in the low-dose females. Serum calcium, which is predominantly bound to albumin, was also decreased ($p<0.01$ or NS) in the high-dose males and females, but the effect in females was only observed during week 7. Triglycerides were increased or decreased in all treated males, but this effect was not dose-dependent.

The LOAEL is 75 mg/kg/day, based on treatment-related clinical findings in both sexes and dose-response decreases in albumin (males) and total protein concentrations (females). The NOAEL is 25 mg/kg/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3150; OECD 409) for a subchronic oral toxicity study in dogs.

Developmental Toxicity

Adequacy of Database for Prenatal Developmental Toxicity: The database for prenatal developmental toxicity is considered incomplete. There is one developmental toxicity study in the rat (MRID 44364920) in the Agency's hazard database, and a brief summary of the reviewed study is provided below.

No developmental toxicity study in the rabbit is available for BBIT. The Agency does not believe that a developmental toxicity study in the rabbit for BBIT would provide more conservative data compared to those of other isothiazolinone chemicals. Therefore, a developmental toxicity study in the rabbit is not anticipated to be required for the BBIT registration review, based on the currently registered uses. Should new use(s) be added and/or current labels be amended, a developmental toxicity study in the rabbit may be required.

870.3700 Prenatal Developmental Toxicity (Gavage) Study – Rat

In a developmental toxicity study (MRID 44364920), 24 presumed pregnant Alpk:AP_fSD (Wistar derived) rats per group were administered 1,2-Benzisothiazolin-3-one, 2-butyl-(95.5%; Batch No. JM 5420/80) by gavage in corn oil at doses of 0, 30, 100, or 300 mg/kg/day on gestation days (GD) 7-16, inclusive. All doses were adjusted for purity. On GD 22, dams were

sacrificed, subjected to gross necropsy, and all fetuses examined externally, viscerally, and skeletally.

No treatment-related deaths occurred during the study but several intercurrent deaths due to gavage error were observed. All remaining animals survived to scheduled sacrifice. Treatment-related clinical signs of toxicity among surviving animals were limited to abnormal respiratory noise in 4/24 high-dose dams on GD 8-19 compared with none in the controls or other treated groups.

Body weights, body weight gains, and food consumption by the low- and mid-dose groups were similar to the controls throughout the study. Adjusted (based on GD 7) body weights of the high-dose group were significantly ($p \leq 0.05$ or 0.01; 96-99% of controls) less than that of the controls from GD 8 through GD 19. Body weight gain by the high-dose group was 82% of the control group level during the dosing interval and reflects slightly (n.s.) lower gravid uterine weights for these dams. Food consumption by the high-dose group was 83-86% ($p \leq 0.01$) of that of the controls during the treatment interval.

At the scheduled gross necropsy, ulcerated areas of the stomach were observed in 0, 1, 5, and 16 animals in the control, low-, mid-, and high-dose groups, respectively. In addition, the mid-dose animal which died also had ulcerated areas of the stomach. These lesions were considered to be indicative of local irritation from the test compound. No other treatment-related lesions were observed in any animal.

Therefore, the maternal toxicity LOAEL for the test compound in rats is 100 mg/kg/day based on ulcerated areas of the stomach. The maternal toxicity NOAEL is 30 mg/kg/day.

No treatment-related differences were observed between the treated and control groups for number of corpora lutea, numbers of implantation and resorption sites, pre- or post-implantation losses, gravid uterine weights, fetal body weights, number of fetuses/litter, or fetal sex ratios. No surviving dam had complete litter resorption.

The total number of fetuses (litters) examined for external, visceral, and skeletal malformations/ variations was 346(24), 272(22), 273(22), and 298(23) in the 0, 30, 100, and 300 mg/kg/day groups, respectively. No treatment-related external, visceral, or skeletal malformations/ variations were observed in any group.

Therefore, the developmental toxicity NOAEL for the test compound in rats is ≥300 mg/kg/day (HDT) and the developmental toxicity LOAEL is not identified.

This study is classified as **Acceptable/Guideline** and satisfies the requirements for a developmental toxicity study [870.3700 (§83-3)] in rats.

Reproductive Toxicity

Adequacy of Database for Reproductive Toxicity: The database for reproductive toxicity is adequate. There is a two-generation reproductive toxicity study for BBIT (MRID 48261201) in the Agency's hazard database; a brief summary of the reviewed study is provided below.

870.3800 Reproduction and Fertility Effects – Rat

In a two-generation reproduction toxicity study (MRID 48261201), *N*-butyl benzisothiazolin-3-one (99.4±1%; Batch # 6180) was administered continuously in the diet to 30 Sprague-Dawley rats/sex/dose group at dietary levels of 0, 300, 600, or 1700 ppm (equivalent to 0/0, 25/27, 49/56, and 141/157 mg/kg/day in males/females, respectively) for two consecutive generations. The P and F1 generation animals were exposed to the test diets for a minimum of 70 days prior to mating. F1 offspring selected to be parents of the F2 generation (30/sex/dose group) were fed the same test diet concentrations as their parents beginning on PND 21. The F2 offspring were terminated after weaning.

All P generation parents survived to scheduled sacrifice. Three F1 adults were found dead or sacrificed during the study; however, none of these mortalities were related to treatment. All other F1 adults survived to scheduled sacrifice.

In the P generation at high-dose level, overall pre-mating (Weeks 0-10) body weight gain was decreased significantly ($p<0.05$) in the females, but was not significantly different from controls in the males. Mean P generation maternal body weights, body weight gains, absolute (g/animal/day) and relative (g/kg/day) food consumption, and food efficiency (%) were unaffected by treatment during gestation.

In the F1 generation at high-dose level, body weights were decreased significantly throughout the pre-mating period (Weeks 18-28) in the males ($p<0.05$) and in the females ($p<0.01$). Overall pre-mating body weight gains were similar to controls at all doses in both sexes. Absolute food consumption was decreased ($p<0.05$) during Weeks 18-19 ($p<0.01$) through 22-23 and 25-26 for males and females, respectively. Relative food consumption was similar to controls for both males and females. Food efficiency was similar to controls for males throughout the pre-mating period but increased ($p<0.05$) during Week 18-19 for females.

Mean F1 generation maternal body weights were decreased at high-dose level during gestation. However, these decreases did not attain statistical significance and there were no significant decreases in body weight gains during gestation. These decreases in body weight were considered to be a continuation of the lower mean body weights noted for these females during pre-mating. Overall body weight gains during gestation were similar to controls at all doses. Mean F1 maternal absolute and relative food consumption and food efficiency were unaffected by treatment during gestation. Overall body weight gains, mean F1 maternal absolute and relative food consumption, and food efficiency were unaffected by treatment during lactation.

No adverse effects of treatment were noted at low- or mid-dose level in either generation.

The LOAEL for parental toxicity is 1700 ppm (equivalent to 141/157 mg/kg/day in males/females, respectively) based on decreased body weights and food consumption. The NOAEL is 600 ppm (equivalent to 49/56 mg/kg/day in males/females, respectively).

No adverse clinical signs were observed in the F1 or F2 generation pups from birth to PND 21 at any dose. No treatment-related differences in litter parameters were noted at any dose in either generation. Sexual maturation was unaffected by treatment. There were no treatment-related effects on gross pathology or histopathology.

At high-dose level, body weights were decreased ($p<0.05$) in the F1 generation and the F2 generation on PND 21. Overall (PND 1-21) pup body weight gains were decreased in both males and females of both generations.

In the F2 generation pups, treatment-related decreases ($p<0.05$) in absolute and relative (to body) spleen weights were observed in both sexes on PND 21.

The LOAEL for offspring toxicity is 1700 ppm (equivalent to 141/157 mg/kg/day in males/females, respectively) based on decreased body weights, body weight gains, and spleen weight (F2 pups only). The NOAEL is 600 ppm (equivalent to 49/56 mg/kg/day in males/females, respectively).

No treatment-related effects on the mating, fertility, conception/copulation, or gestation indices were observed in either generation. There were no effects of treatment on pre-coital interval or gestation duration in either generation. No signs of dystocia were noted at any dose. Mean estrous cycle lengths were unaffected by treatment in both generations. No treatment-related effects were observed on P or F1 generation spermatogenesis endpoints (mean testicular and epididymal sperm numbers, sperm production rate, motility, progressive motility, and morphology).

The LOAEL for reproductive toxicity was not observed. The NOAEL is 1700 ppm (equivalent to 141/157 mg/kg/day in males/females, respectively).

This study is classified as A**cceptable/Guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

Chronic Toxicity

Adequacy of Database for Chronic Toxicity: There are no chronic toxicity studies in the Agency's hazard database for BBIT; the data were bridged from other isothiazolinone chemicals when the toxicology endpoints were revised recently. The studies are not anticipated to be required, at present, for BBIT registration review risk assessment, based on the currently registered uses. However, should new use(s) be added and/or current labels be amended, these studies may be required.

Carcinogenicity

Adequacy of Database for Carcinogenicity: There are no carcinogenicity studies in the Agency's hazard database for BBIT; the data were bridged from other isothiazolinone chemicals when the toxicology endpoints were revised recently. The studies are not anticipated to be required, at present, for BBIT registration review risk assessment, based on the currently registered uses. However, should new use(s) be added and/or current labels be amended, these studies may be required.

Mutagenicity

Adequacy of Database for Mutagenicity: The database for mutagenicity is considered adequate. Several mutagenicity studies have been submitted and found to be acceptable by the Agency. The summaries of these studies are provided below.

Gene Mutation

870.5300 *In Vitro* Mammalian Cell Gene Mutation Test

In a mammalian cell gene mutation assay at the TK locus (MRID 44364923), mouse lymphoma L5178Y $TK^{\pm}$ cells cultured *in vitro* were exposed to 1,2-Benzisothiazolin-3-one, 2-butyl (BBIT; 95.5% a.i. w/w; Batch No. Blend JM5420/80) in DMSO in three independent assays. In the first assay cells were exposed at concentrations of 0.2, 0.4, 0.8, 1.6, 3.1 µg/mL in the absence of metabolic activation (S9-mix) and to concentrations of 1.6, 3.1, 6.3, 12.5, 25.0 µg/mL in the presence of S9-mix. In the second assay cells were exposed to concentrations of 0.1, 0.2, 0.4, 0.8, 1.6 µg/mL without S9-mix and to concentrations of 3.1, 6.3, 12.5, 25, 50 µg/mL with S9-mix. In the third assay cells were exposed to concentrations of 0.4, 0.5, 0.6, 0.8, 1.1, 1.5, 2.0 µg/mL without S9-mix only. The S9-fraction was obtained from phenobarbital and β-naphthoflavone induced male Sprague-Dawley rat liver.

BBIT was tested up to cytotoxic concentrations. In the first assay in the absence of S9-mix, the mean mutant frequencies ranged from 2.7×10^{-4} to 3.7×10^{-4} at concentrations ranging from 0.2 to 1.6 µg/mL compared to the solvent control value of 3.5×10^{-4}. In the presence of S9-mix, the mean mutant frequencies ranged from 1.1×10^{-4} to1.7×10^{-4} from the lowest to the highest concentration tested compared to the solvent control value of 1.2×10^{-4}. Results from the second and third assays were comparable to those of the first. The mutant frequency of treated cells was not considered significantly increased over the respective solvent control value at any point in this study and no statistical analysis was done. The solvent and positive controls induced the appropriate responses. **There was no evidence of induced mutant colonies over background.**

This study is classified as **Acceptable/Guideline**. It satisfies the requirement for FIFRA Test Guideline (OPPTS 870.5300 [§84-2]) for *in vitro* mutagenicity (mammalian forward gene mutation) data.

870.5375 *In Vitro* Mammalian Chromosome Aberration Test

In an *in vitro* mammalian cell cytogenetic (chromosomal aberration) assay (MRID 44364922), human lymphocyte cultures were cultured for 48 hours, exposed to 1,2-Benzisothiazolin-3-one, 2-butyl (BBIT; 95.5% a.i. w/w; Batch No. Blend JM5420/80) in DMSO for three hours and then incubated for an additional 17 or 41 hours. Exposures were as follows: Cell donor 1 (female): (68 hour sampling time) nonactivated and activated conditions (S9-mix): 2, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25 µg/mL; Cell donor 2 (male): (68 hour sampling time) without S9-mix: 1, 2, 5, 7.5, 10, 12.5 µg/mL; with S9-mix: 2, 5, 7.5, 10, 12.5, 15, 17.5 µg/mL; Cell donor 2: (92 hour sampling time) without S9-mix: 5, 7.5, 10, 12.5 µg/mL; with S9-mix: 10, 12.5, 15, 17.5 µg/mL. The S9-fraction was obtained from phenobarbital/β-naphthoflavone induced male Sprague-Dawley rat liver.

BBIT was tested up to cytotoxic concentrations. Based on mitotic index determinations, cells from donors 1 and 2 treated at test material concentrations of 2.0, 5.0 and 10.0 without S9-mix and 2.0, 7.5 and 15.0 µg/mL with S9-mix were evaluated for chromosomal aberrations at the 68 hour sampling time. Cells from donor 2 treated at 10.0 µg/mL without S9-mix and at 15.0 µg/mL with S9-mix were evaluated for chromosomal aberrations at the 92 hour sampling time.

Statistically significant increases in mean percentage of cells with aberrations (primarily breaks and fragments) were observed at 92 hours both in the presence and absence of S9-mix. BBIT was clastogenic to human lymphocytes *in vitro* as tested in this study.

This study is classified as **Acceptable/Guideline**. It satisfies the requirement for FIFRA Test Guideline [OPPTS 870.5375 (§84-2) for *in vitro* cytogenetic mutagenicity data.

Cytogenetics

870.5395 *In Vivo* Mammalian Erythrocyte Micronucleus Test

In an *in vivo* bone marrow micronucleus assay (MRID 44364924), Charles River CD-1 albino mice (10/sex) were treated by oral gavage with N-Butyl-1,2-benzisothiazolin-3-one (BBIT; 95.5% a.i.; Batch No. Blend JM5420/80) emulsified in corn oil, at the maximum tolerated doses of 1250 mg/kg (males) or 2000 mg/kg (females). Both males and females were sacrificed at both 24 (5/sex) and 48 (5/sex) hours. A cyclophosphamide positive control (5 mice/sex) was run concurrently and sacrificed at 24 hours. A vehicle control (corn oil) was also run concurrently with 5 animals/sex sacrificed at both 24 and 48 hours. Bone marrow cells were harvested at 24 and 48 hours post-treatment from all groups, except the positive control which was harvested only at 24 hours.

The test substance, BBIT, produced no significant increase in the frequency of bone marrow micronucleated polychromatic erythrocytes at either 24 or 48 hours after treatment. The positive and vehicle controls induced the appropriate response.

BBIT is not considered to be a mutagen under conditions of this study.

This study is classified as **Acceptable/Guideline** and satisfies the requirement for FIFRA Test Guideline § 84-2 for *in vivo* cytogenetic mutagenicity data.

Other Genotoxicity

870.5550 *In Vivo/In Vitro* Unscheduled DNA Synthesis (UDS) in Mammalian Cells

In an *in vivo/in vitro* unscheduled DNA synthesis (UDS) assay (MRID 44364925) in rat hepatocytes, 1,2-benzisothiazolin-3-one, 2-butyl (BBIT; 95.5% a.i. w/w; Batch No. Blend JM5420/80) at doses of 500 and 800 mg/kg, based on the result of a preliminary dose range-finding study, was administered to two or three male Alpk:AP SD rats per test group by oral gavage. BBIT was delivered in corn oil at a volume of 10 mL/kg body weight. Hepatocytes were isolated at 2 or 16 hours post-treatment and cultured for determination of tritiated thymidine incorporation.

No increase in the mean net nuclear grain count or the percentage of cells in repair over the solvent control values was seen at either dose at either harvest time. The solvent and positive control values were appropriate.

The mean net nuclear grain count was below zero for both doses at both treatment times indicating no induction of UDS as tested in this study.

This study was originally classified as an **Unacceptable** study because no evidence was presented that 800 mg/kg was a limiting upper dose and could be upgraded to acceptable if some evidence of cytotoxicity at 800 mg/kg is available but was not reported or if a higher dose is tested. After revisiting the study report, this study is now classified as **Acceptable/Non-guideline**. The deficiency cited before was located in *section 6.1 Phase I – Determination of the maximum tolerated dose* on page 17 of the study report. Significant histopathological changes to the live were observed in the next two higher doses than 800 mg/kg; these two higher doses were considered to be exceeded the maximum tolerated dose (MTD). The animals exposed to 800 mg/kg didn't show such histopathological changes to the live; therefore, 800 mg/kg was selected as the MTD based on target organ toxicity.

Neurotoxicity

870.6200 Neurotoxicity Screening Battery

Adequacy of Database for Neurotoxicity: There are no neurotoxicity studies in the Agency's hazard database. In a 90-day oral (feeding) toxicity in rats (MRID 44403001), there were no treatment-related neurotoxic effects or effects on motor activity observed, in the Functional Observational Battery (FOB) and motor activity conducted. The Agency does not believe that a neurotoxicity screening battery study would provide more conservative hazard data compared to the existing database of the entire isothiazolinone chemicals group. Therefore, a neurotoxicity screening battery is not anticipated to be required for the BBIT registration review risk assessment, based on the currently registered uses. Should new use(s) be added and/or current labels be amended, these studies may be required.

Immunotoxicity

870.7800 Immunotoxicity Study

Adequacy of Database for Immunotoxicity: There are no immunotoxicity studies in the Agency's hazard database. The Agency does not believe that an immunotoxicity study would provide more conservative endpoint compared to the existing database of the entire isothiazolinone chemicals group. Therefore, the Agency waived the requirement of an immunotoxicity study for the isothiazolinone chemicals group.

Other Toxicological Effects

870.7485 Metabolism and Pharmacokinetics

(1) In a tissue distribution time course study (MRID 48262201), [^{14}C]-N-butyl benzisothiazolin-3-one (radiolabelled at the benzene ring, > 98% radiochemical purity, batch # SEL/1653) was administered to 30 male Han Wistar rats, by gavage, at a nominal dose level of 5 mg/kg/day for up to 14 days (equivalent nominal radioactive dose of 27.03 µCi/kg/day). Select tissues were measured for radioactive content for up to 60 days after the last administered dose.

The majority of the administered radioactivity was excreted in the urine and feces. Approximately 87% of the first administered dose and 92% of the 14th administered daily dose were excreted in the urine within 24 hours of dosing, while approximately 15% of the first and 14th doses were excreted in the feces within 24 hours post-dosing.

The tissue distribution of radioactivity following oral dosing with [^{14}C]-N-butyl benzisothiazolin-3-one was widespread; however, the concentrations in individual tissues were all very low. The highest concentrations of radioactivity were found in the G.I. tract plus contents, skin, bladder, residual carcass, liver and kidneys. High concentrations in the G.I. tract and bladder were attributed to the presence of feces and urine in these organs; and high concentrations in the liver and kidneys can be explained because these organs are the major sites of metabolism and excretion for N-butyl benzisothiazolin-3-one. High concentrations in the skin and residual carcass (0.440 and 0.201 µg equivalents/g of tissue, respectively) can be explained by lipophilic deposits in these tissues. After termination of dosing, the concentrations of radioactivity in the majority of tissues declined rapidly and reached background levels within 7 days. Concentrations of radioactivity in the liver, kidneys, skin, and residual carcass were slower to decline but only those in the skin and residual carcass were measurable by 60 days after last dose. The calculated elimination half-lives of N-butyl benzisothiazolin-3-one from the skin and residual carcass were 29.6 and 27.4 days, respectively. There was no evidence to suggest persistence of N-butyl benzisothiazolin-3-one in any of the tissues or organs that were examined.

This tissue distribution time course study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a Tier 2 metabolism and pharmacokinetics study [OPPTS 870.7485] in the rat.

(2) This summary includes a metabolism study (MRID48349201) and a metabolite identification study (MRID48262203) with N-butylbenzisothiazolin-3-one.

In a metabolism study (MRID 48349201), ^{14}C-radiolabelled N-butyl benzisothiazolin-3-one (>98% a.i., batch # SEL/1653) was administered to male Han Wistar rats (4/dose for pharmacokinetic study, 2/dose for expired air study, 4/dose for excretion balance study, and 20/dose for tissue depletion study) via a single oral dose at levels of 5 or 300 mg [^{14}C]-BBIT/kg. For the metabolite identification study (MRID48262203), 14 repeated doses of 5 mg [^{14}C]-BBIT/kg were also given.

Peak concentrations of [^{14}C]-BBIT were measured in blood of rats 1 hour and 4 hours, respectively, following oral administration of the 5 mg/kg or 300 mg/kg doses. Blood concentrations declined quickly and were below the limits of detection within 48 hours for both doses. The greatest concentrations of radioactivity were seen in the bladder and GI tract within 1 hour and 4 hours post dosing and declined rapidly within 48 hours for both doses. Residual radioactivity 3 days post-dosing, accounting for 0.3% of the total administered dose, was seen in the lymph nodes, abdominal fat, pancreas, skin, residual carcass, liver, and kidney. The majority of the administered doses were excreted in the urine and feces, negligible amounts were detected in expired air. Overall, tissue distribution and elimination profiles for the 5 mg/kg and 30 mg/kg dose were similar.

Metabolism of [^{14}C]-BBIT following oral administration of 5 mg [^{14}C]-BBIT/kg or 300 mg [^{14}C]-BBIT/kg in rats is similar and essentially complete with only small amounts of un-metabolized test substance (<0.5% of administered doses) being detected in the urine and feces. Only trace amounts of metabolites were detected in expired air. The predominant urinary metabolites of [^{14}C]-BBIT were identified as a methyl sulfoxide derivative (Metabolite 5, 26-27% of dose), an S-glucoronide metabolite (Metabolite 7, 23-24% of dose), and a methyl sulfoxide metabolite of BBIT with carbonyl substitution (Metabolite 11, 11-18% of dose). These metabolites were also detected in the feces, although at lower and more variable concentrations. Based on the identified metabolites of BBIT, its metabolism is thought to occur via two major routes. Route one involves opening of the isothiazoline ring followed by conjugation of the sulfur atom with glucuronic acid. Route two involves direct oxidation and methylation of the sulfur atom in the isothiazoline rings forming the methyl sulphoxide which then undergoes further oxidation of the N-alkyl side chain and/or N-demethylation.

For the 14-day repeated 5 mg/kg doses study (MRID48262203), urinary metabolite profiles were qualitatively similar between samples collected over 24 hours after the first and final doses and consistent with the single 5 mg/kg dose test results. Same similarity was found for fecal metabolite profiles for samples collected over 24 hours after the first and final doses; however, higher amount of parent material and metabolite 6 were observed following repeated dosing.

The metabolism study (MRID48349201) in the rat is classified as **acceptable** and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

The metabolism study (MRID 48262203) in the rat is classified **acceptable** and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

Table A2 – Toxicity Profile for BBIT

Guideline No./ Study Type	MRID No./ Study Classification	Dosing and Animal Information	Results
Subchronic Toxicity			
870.3100 90-day Oral (Rat)	MRID 44403001 Acceptable/Guideline	Purity 95.5% 20 Wistar-derived Sprague Dawley (Alpk:APfSD) rats/sex/dose 0, 40, 200, and 2000 ppm (♂/♀: 0/0, 3.1/3.4, 15.3/16.6, or 149.2/162.4 mg/kg/d), in feed, for 90 days	**NOAEL = 200 ppm (♂/♀: 15.3/16.6 m/k/d)** **LOAEL = 2000 ppm (♂/♀:** 149.2/162.4 **m/k/d)**, based on submucosal inflammation of the stomach
870.3150 90-day Oral (Dog)	MRID 48262204 Acceptable/Guideline	Purity 99.4% 4 Beagle dogs/sex/dose 0, 25, 75, or 250/200 mg/kg/d, gelatin capsule, once daily, for at least 90 days. The high dose was reduced to 200 mg/kg/day beginning on Day 10 due to one female who was sacrificed *in extremis* at 250 mg/kg/day.	**$NOAEL_{male}$ = 25 mg/kg/d** **$NOAEL_{female}$ = 75 mg/kg/d**, based on treatment-related clinical findings in both sexes and dose-response decreases in albumin (males) and total protein concentrations (females)
Developmental Toxicity			
870.3700 Developmental Toxicity (Rat)	MRID 44364920 Acceptable/Guideline	Purity 95.5% 24 presumed pregnant Alpk:AP_fSD (Wistar derived) rats/dose 0, 30, 100, or 300 mg/kg/d, GD 7–16	**$NOAEL_{maternal}$ = 30 mg/kg/d** **$LOAEL_{maternal}$ = 100 mg/kg/d**, based on ulcerated areas of the stomach **$NOAEL_{developmental} \geq$ 300 mg/kg/d** (highest dose tested [HDT]). **$LOAEL_{developmental}$ not established**.
Reproduction Toxicity			
870.3800 Reproduction	MRID 48261201 Acceptable/Guideline	Purity 99.4±1% 30 Sprague-Dawley rats/sex/dose; 0, 300, 600, or 1700 ppm (♂/♀: 0/0, 25/27, 49/56, or 141/157 mg/kg/d), in diet	**$NOAEL_{parental}$ = 600 ppm (♂/♀: 49/56 mg/kg/d)** **$LOAEL_{parental}$ = 1700 ppm (♂/♀:** 141/157 **mg/kg/d)**, based on decreased body weights and food consumption **$NOAEL_{offspring}$ = 600 ppm (♂/♀: 49/56 mg/kg/d)** **$LOAEL_{parental}$ = 1700 ppm (♂/♀:** 141/157 **mg/kg/d)**, based on decreased body weights, body weight gains, and spleen weight (F2 pups only) **$NOAEL_{reproductive} \geq$ 1700 ppm (♂/♀:** 141/157 **mg/kg/d)** (HDT); **$LOAEL_{reproductive}$ not established**

Guideline No./ Study Type	MRID No./ Study Classification	Dosing and Animal Information	Results
Chronic Toxicity			
870.4100 Chronic Toxicity	A chronic toxicity study is not available for BBIT.		
Carcinogenicity			
870.4200 Carcinogenicity	A carcinogenicity study is not available for BBIT.		
Mutagenicity			
870.5300 *In vitro* Mammalian cell gene mutation test	MRID 44364923 Acceptable/Guideline	Purity 95.5% mouse lymphoma cells (L5178Y $TK^{+/-}$) In the 1st assay: 0.2, 0.4, 0.8, 1.6, or 3.1 µg/mL, -S9; 1.6, 3.1, 6.3, 12.5, or 25.0 µg/mL, +S9; In the 2nd assay: 0.1, 0.2, 0.4, 0.8, or 1.6 µg/mL, -S9; 3.1, 6.3, 12.5, 25.0, or 50 µg/mL, +S9; In the 3rd assay: 0.4, 0.5, 0.6, 0.8, 1.1, 1.5, or 2.0 µg/mL, -S9	**Negative**
870.5375 *In vitro* Mammalian cytogenetics (chromosome aberration) test	MRID 44364922 Acceptable/Guideline	Purity 95.5% human lymphocyte cultures Cell donor 1 (♀) (68 hour sampling time): 2, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25 µg/mL, ±S9; Cell donor 2 (♂) (68 hour sampling time): 1, 2, 5, 7.5, 10, 12.5 µg/mL, -S9; 2, 5, 7.5, 10, 12.5, 15, 17.5 µg/mL, +S9; Cell donor 2 (♂) (92 hour sampling time): 5, 7.5, 10, 12.5 µg/mL, -S9; 10, 12.5, 15, 17.5 µg/mL, +S9	**Positive (±S9)**
870.5395 *In vivo* mammalian Erythrocyte Micronucleus test (mouse)	MRID 44364924 Acceptable/Guideline	Purity 95.5% Charles River CD-1 albino mice (10/sex) max. tolerated doses of 1250 mg/kg (♂) and 2000 mg/kg (♀) in corn oil, oral gavage; both males and females were sacrificed at	**Negative**

Guideline No./ Study Type	MRID No./ Study Classification	Dosing and Animal Information	Results
		both 24 (5/sex) and 48 (5/sex) hours.	
870.5550 (*In vivo/in vitro*) Unscheduled DNA synthesis	MRID 44364925 Acceptable/ Nonguideline	Purity 95.5% Rat hepatocyte cells 0, 500, or 800 mg/kg in corn oil in a vol. of 10 mL/kg bd wt, 2 (500 mg/kg) or 3 (800 mg/kg) male Alpk:AP SD rats, oral gavage; hepatocytes were isolated at 2 or 16 hours post-treatment	**Negative**
Metabolism			
870.7485 Metabolism and Pharmacokinetics	MRID 48262201 Acceptable/Guideline	Purity >98% (radiolabeled) 30 male Han Wistar rats nominal dose level of 5 mg/kg/day (equivalent nominal radioactive dose of 27.03 µCi/kg/day), oral gavage, for up to 14 days. Select tissues were measured for radioactive content for up to 60 days after the last administered dose.	Approximately 87% of the first administered dose and 92% of the 14th administered daily dose were excreted in the urine within 24 hours of dosing, while approximately 15% of the first and 14th doses were excreted in the feces within 24 hours post-dosing. The highest concentrations of radioactivity were found in the G.I. tract plus contents, skin, bladder, residual carcass, liver and kidneys. After termination of dosing, the concentrations of radioactivity in the majority of tissues declined rapidly and reached background levels within 7 days. Concentrations of radioactivity in the liver, kidneys, skin, and residual carcass were slower to decline but only those in the skin and residual carcass were measurable by 60 days after last dose. The calculated elimination half-lives of BBIT from the skin and residual carcass were 29.6 and 27.4 days, respectively. There was no evidence to suggest persistence of BBIT in any of the tissues or organs that were examined.

Guideline No./ Study Type	MRID No./ Study Classification	Dosing and Animal Information	Results
870.7485 Metabolism and Pharmacokinetics	MRIDs 48349201 & 48262203 Acceptable/Guideline	Purity >98% (radiolabeled); Han Wistar male rats (4/dose for pharmacokinetic study, 2/dose for expired air study, 4/dose for excretion balance study, and 20/dose for tissue depletion study) via a single oral dose at levels of 5 or 300 mg [^{14}C]-BBIT/kg. For the metabolite identification study (MRID 48262203), 14 repeated doses of 5 mg [^{14}C]-BBIT/kg were also given.	Peak concentrations of [^{14}C]-BBIT were measured in blood of rats 1 hour and 4 hours, respectively, following oral administration of the 5 mg/kg or 300 mg/kg doses; then declined quickly and were below the limits of detection within 48 hours for both doses. The greatest concentrations of radioactivity were seen in the bladder and GI tract within 1 hour and 4 hours post dosing and declined rapidly within 48 hours for both doses. Residual radioactivity 3 days post-dosing, accounting for 0.3% of the total administered dose, was seen in the lymph nodes, abdominal fat, pancreas, skin, residual carcass, liver, and kidney. The majority of the administered doses were excreted in the urine and feces, negligible amounts were detected in expired air. Overall, tissue distribution and elimination profiles for the 5 mg/kg and 30 mg/kg dose were similar. The predominant urinary metabolites of [^{14}C]-BBIT were identified as a methyl sulfoxide derivative (Metabolite 5, 26-27% of dose), an S-glucoronide metabolite (Metabolite 7, 23-24% of dose), and a methyl sulfoxide metabolite of BBIT with carbonyl substitution (Metabolite 11, 11-18% of dose). These metabolites were also detected in the feces, although at lower and more variable concentrations. Urinary metabolite profiles were qualitatively similar for the 14-day repeated 5 mg/kg doses study (MRID 48262203). However, higher amount of parent material and metabolite 6 were observed following repeated dosing.

Toxicology References for Appendix A

MRID 44364915 Lees, D. (1996) Substance S123386: Acute Oral Toxicity Study in Rats: Lab Project Number: AR6193: CTL/P/5067. Unpublished study prepared by Central Toxicology Lab. (Zeneca) 91 p.

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MRID 44364917 Lees, D. (1996) Substance S123386: Skin Irritation to the Rabbit: Lab Project Number: CTL/P/4969: EB4412. Unpublished study prepared by Central Toxicology Lab. (Zeneca) 20 p.

MRID 44364918 Lees, D. (1996) Substance S123386: Skin Sensitisation to the Guinea Pig: Lab Project Number: CTL/P/5046: GG6736. Unpublished study prepared by Central Toxicology Lab. (Zeneca) 34 p.

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MRID 44364922 Wildgoose, J. (1996) Substance S123386: in vitro cytogenetic assay in human lymphocytes. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, SK10 4TJ. Laboratory Project ID: Report No. CTL/P/5037, Study No. SV0800, July 11, 1996. MRID 44364922. Unpublished.

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MRID 44364924 Fox, V., Substance S123386: Mouse Bone Marrow Micronucleus Test. Central Toxicology Laboratory, Cheshire, UK. Report No. CTL/P/5171. Study No. SM0801. Sept. 19, 1996. MRID 44364924. Unpublished.

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MRID 44403001 Rattray, N. J. (1997) Substance S123386: 90 day feeding study in rats (Dolphin Fungicide). Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, SK10 UTJ, Report No. CTL/P/5280, February 12, 1997. MRID 44403001. Unpublished.

MRID 45083004 Rattray, N. (1997) DS 6039: 4-Hour Acute Inhalation Toxicity Study in Rats: Lab Project Number: CTL/P/5556: HR2306. Unpublished study prepared by CTL, Inc. 87 p.

MRID 48261201 Stump, D.G. (2007) A dietary two-generation reproductive toxicity study of *N*-butyl benzisothiazolin-3-one in rats. WIL Research Laboratories, LLC, Ashland, OH. Laboratory Study No.: WIL-544004, April 16, 2007. MRID 48261201. Unpublished.

MRID 48262201 Smith, A.D. (2006) N-butyl benzisothiazolin-3-one: Repeat dose study in the rat (metabolism and pharmacokinetics). Syngenta Limited (CTL), Cheshire, UK. Laboratory Project ID: Syngenta Number CO04375rl,Report ID: UR0884-REG, October 6, 2006. MRID 48262201. Unpublished.

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MRID 48349201 Smith, A.D. (2006). N-Butyl Benzisothiazolin-3-One: Absorption, Distribution, Metabolism and Excretion in the Rat. Syngenta Limited (CTL). Laboratory Project ID: CO04375r1, Report ID: UR0868-REG, October 6, 2006. MRID 48349201. Unpublished.

Appendix B Environmental Fate

Environmental Fate and Transport Properties of Butyl BIT (N-butyl-1,2-Benzisothazolin-3-one (BBIT) and its Transformation Products

Water and Sediment

Hydrolysis

Butyl BIT (BBIT) is hydrolytically stable for 6 days with an expected half-life of >1 year under abiotic and buffered conditions at pH 5, 7, and 9 and 50 ^{o}C. Based on these results, BBIT is expected to be stable at 25 ^{o}C (MRID 44364926). The related compound, BIT, was also stable at 25 ^{o}C at pH 5, 7, and 9 (MRIDs 41199101, 44182101).

Aqueous Photolysis

In aqueous photolysis, BIT degraded at pH 5 with a half-life of 9 hours, while at pH 7 and 9, the half-life was 0.7 hours. Six photodegradation products were identified, including two transformation products with an intact benzene ring and an intact isothiazolinone ring. These two transformation products with two (2) intact rings were hydroxy-1,2-benzisothiazol-3-one (hydroxylated BIT) and saccharin (BIT sulfone). The half-lives for the sum of parent BIT and these two transformation products with two intact ring structures were all about 1 day at pH 5, 4.9 days at pH 7, and 9.8 days at pH 9, but residues were present until the end of the study (30 days).

The 2-sulfobenzamide molecule (ortho sulfobenzamide), which contains an intact benzene ring but not an intact isothiazolinone ring, reached maximum concentrations of 22.7 % at pH 5, 53 % at pH 7, and 37 % at pH 9 by the end of the study. The transformation product, 1,2-benzthiazolin-2-one contained an intact benzene ring and a rearranged isothiazolinone ring, and reached 50 % of BIT by the end of the study at pH 5. However, 1,2-benzthiazolin-2-one did not reach significant concentrations at pH 7 and 9 (MRID 47329402).

Data on photodegradation of BBIT in water are not anticipated to be required because the additional 4-carbon side chain is not likely to affect the rate of photodegradation.

Octanol-Water Partition Coefficient and Bioconcentration in Aquatic Organisms

The measured values of log K_{ow} are 2.32 (unitless) for BBIT and 1.4 (unitless) for BIT (Table 4) and the estimated values for the transformation products in Table E3 range from -3.16-1.76. Based on these log Kow values, which are lower than a log K_{ow} of 3, indicating low potential for bioconcentration, BBIT, BIT and the transformation products are not likely to be

bioaccumulative in aquatic species, and bioconcentration data are not anticipated to be required for BIT or BBIT.

Aerobic Aquatic Metabolism

Data were required for BIT in the Final Work Plan (December, 2014). Aerobic aquatic metabolism data may be generated for either compound and bridging is appropriate based on the similarity in chemical structure.

Anaerobic Aquatic Metabolism

For BIT, data on anaerobic aquatic metabolism were not required because of the relatively low sorption of BIT to soil and sediment. For BBIT, these data are also not required based on the structural similarity between BIT and BBIT.

Soil

Soil Leaching/Adsorption/Desorption Batch Equilibrium

A leaching-adsorption-desorption study for BIT demonstrated K_d values of 1.24-9.56 L/kg and K_{oc} values of 235-566 L/kg, and based on the K_{oc} values and FAO classification system[10], BIT is considered to be moderately mobile in soil (MRID 41687102). For BBIT, these data are also not required based on the structural similarity between BIT and BBIT.

Aerobic Soil Metabolism

In the aerobic soil metabolism study, the half-life of BIT was reported to be less than one day (MRID 41199102). However, there is uncertainty about the persistence and occurrence of the transformation products since the percent formation of 2-sulfobenzamide, BIT sulfoxide, and BIT sulfone, was only quantified at day 7 and day 28 of a 180-day study (MRID 41199103). Two major metabolites were identified; 2-sulfobenzamide (ortho sulfobenzamide) and BIT-S-oxide (also known as BIT sulfoxide). Aerobic soil metabolism data are not anticipated to be required for BBIT because of the structural similarity between BIT and BBIT.

Fate and Transport in WWTP

Activated Sludge Sorption Isotherm

The measured values of log K_{ow} are 2.32 (unitless) for BBIT and 1.4 (unitless) for BIT (Table 4) and the estimated values for the transformation products in Table E3 range from -3.16-1.76. Based on these log K_{ow} values, which are lower than a log K_{ow} of 3, indicating low potential for sorption to activated sludge, BBIT, BIT and the transformation products are not expected to be likely to sorb to activated sludge. Therefore, an activated sludge sorption isotherm (ASSI) study for BBIT is not required.

[10] http://www.fao.org/docrep/003/x2570e/x2570e06.htm

Activated Sludge Respiration Inhibition

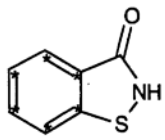
For BIT, the IC_{50} was 30 mg/L and the IC_{50} for the reference substance, 3,5-dichlorophenol, was 12 mg/L (MRID 47759819). ASRI data are not required for BBIT because of the structural similarity between BIT and BBIT.

Activated Sludge Biodegradation

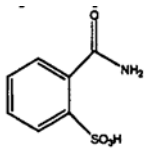
Data on biodegradation in activated sludge were required for BIT in the December 2014 Final Work Plan. Biodegradation data may be generated for either BIT or BBIT, and bridging from BIT is appropriate based on the similarity in chemical structure.

A number of transformation products have been identified and characterized for the parent BIT. Similar transformation products would be expected for BBIT.

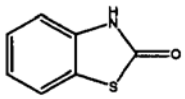
The transformation products of BIT from photodegradation in water and aerobic soil metabolism studies include:



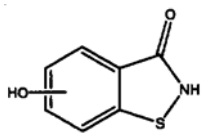
BIT (1,2-benzisothiazol-3(2H)-one)



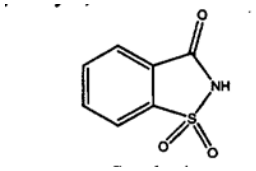
2-sulfobenzamide (orthosulfobenzamide)



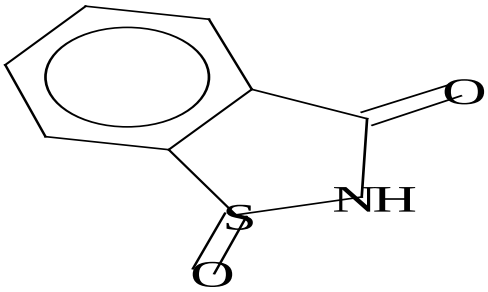
1,2-benzthiazolin-2-one



Hydroxy-1,2-benzisothiazol-3-one



Saccharin (1,2-benzisothiazolin-3-one-1,1-dioxide)



BIT-S-Oxide

Table B1 below presents the environmental fate and transport properties of BBIT and BIT.

Table B1. Environmental Fate and Transport Properties of BBIT and BIT

Property (Guideline number)	**Value**	**Reference (MRID unless specified)** **Comments**
Hydrolysis (161-1, 835.2120)	Stable at 5, 7, and 9	44364926 (BBIT) 47329401 (BIT)
Photodegradation in water (161-2, 835.2210)	Stable in dark controls 9 hours (pH 5), 0.7 hours (pH 7 and 9)	47329402 (BIT) Data for BBIT not required Major transformation products Ortho-sulfobenzamide 1,2-benzthiazolin-2-one hydroxy-1,2-benzisothiazolin-3-one (hydroxy BIT) Saccharin

Aerobic soil metabolism (162-1, 835.4100)	Half-life of <1 day for BIT (observed) 90 % dissipation of BIT by 7-28 days and 98-99 % dissipation by 60-180 days	41199102 and 41199103 (BIT) Data for BBIT not required Ortho-sulfobenzamide and BIT-S-oxide were significant transformation products
Leaching-Adsorption-Desorption (163-1, 835.1230)	 Kads (Kocs) in L/Kg 2.5 (486) 1.3 (254) 12.2 (728) 2.5 (389)	41687102 (BIT) BIT data is bridgeable to BBIT Loamy sand Loam Silty clay loam Silt loam
Anaerobic aquatic metabolism (162-4, 835.4400	Not required (BIT and BBIT)	Waived for BIT because of lack of sorption Also waived for BBIT because of structural similarity between BIT and BBIT
Aerobic aquatic metabolism (162-3, 835.4300)[11]	Required (BIT or BBIT)	Data on aerobic aquatic metabolism were required in December 2014 Final Work Plan for BIT BIT data is bridgeable to BBIT
Activated Sludge Sorption Isotherm (ASSI)	Not required (BIT and BBIT)	Not required because measured log Kow values for BIT (1.4) and BBIT (2.32) are less than 3 (Table E3)
Activated Sludge Respiration Inhibition (ASRI, 850.6800, OECD 209)[12]	For BIT EC_{50} = 30 mg/L EC_{20} = 11.5 mg/L EC_{80} = 79 mg/L. NOEC = 1 (one) mg/L.	47759819 (BIT) BIT data is bridgeable to BBIT
Biodegradation in wastewater treatment plants (835.3110, 835.3220, 835.3240, 835.3280)[11]	Required (BIT or BBIT)	BIT data is bridgeable to BBIT

[11] Biodegradation or Aerobic aquatic metabolism data may be generated for either compound and bridging is appropriate based on the similarity in chemical structure.

[12] For BIT, based on an ASRI value of 30 mg/L (>20 mg/L), the registrant must conduct either: (i) Ready Biodegradability or (ii) a) Biodegradation in Activated Sludge or b) Simulation Test - Aerobic Sewage Treatment: A. Activated Sludge Units or c) the Porous Pot Test. If the Ready Biodegradability study is conducted and passes, then no further testing is required. If, however, the antimicrobial fails the Ready Biodegradability study, then the a) Biodegradation in Activated Sludge or b) Simulation Test - Aerobic Sewage Treatment: A. Activated Sludge Units, or c) the Porous Pot study is required.

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MRID 47759819. Schaefer, E.; Matthews, M. (2006) 1,2-Benzisothiazolin-3-One: An Activated Sludge, Respiration Inhibition Test. Project Number: 129E/120, 06RC/088, 129/041806/ASRT/SUB129. Unpublished study prepared by Wildlife International, Ltd. 37p.

MRID 47759821. Stenzel, J.; Schaefer, E. (2007) 1,2-Benzisothiazolin-3-One: Soil Microorganisms: Nitrogen Transformation Test. Project Number: 129E/119, 06RC/096. Unpublished study prepared by Wildlife International, Ltd. 49 p.

MRID 47759822. Stenzel, J.; Schaefer, E. (2007) 1,2-Benzisothiazoline-3-One: Soil Microorganisms: Carbon Transformation Test. Project Number: 129E/118, 06RC/097. Unpublished study prepared by Wildlife International, Ltd. 43 p.

Appendix C Ecotoxicology Profile

As indicated in sections 4.1 and 4.3, data from BIT are being bridged to BBIT and will be used for the risk assessment.

Toxicity to Terrestrial Organisms

Birds

One acceptable acute-oral (LD50) study categorizes BIT as being moderately toxic to birds. The guideline (850.2100) is satisfied. Avian dietary studies (850.2200) are not required for BIT. However, one study was previously submitted and indicates that BIT is practically nontoxic when administered in the diet.

Avian Acute-oral and Dietary Toxicity

Test Species	Test Material (% ai)	Toxicity	Toxicity Category	MRID
Northern bobwhite (*Colinus virginianus*)	99	LD50 = 453mg ai/kg bw	Moderately toxic	409913-01 Acceptable
	72.2	LC50 >5620 ppm	Practically non-toxic	417320-01 Acceptable

Nontarget Insects

Toxicity data for beneficial insects (850.3020, 850.3030) are not needed to support the current use patterns, because BIT is not registered as a wood preservative.

Toxicity to Aquatic Organisms

Freshwater Fish, acute

The available acute toxicity studies categorize technical-grade BIT as being moderately to highly toxic to freshwater fish. The guideline (850.1075) for acute toxicity testing is satisfied.

Acute Toxicity to Freshwater Fish

Test Species	Test Material (% ai)	Toxicity Endpoint (mg ai/L)	Toxicity Category	MRID
Rainbow Trout (*Oncorhynchus mykiss)*	73.62	LC50 = 1.3	Moderately toxic	455346-02 Acceptable
	93	LC50 = 1.6	Moderately toxic	416871-01 Acceptable
	89.9	LC50 = 1.9	Moderately toxic	473190-10 Acceptable
Bluegill (*Lepomis macrochirus*)	93.2	LC50 = 0.54	Highly toxic	443649-13 Acceptable

Freshwater Invertebrates, acute

Three available acute toxicity studies categorize technical-grade BIT as being moderately to very highly toxic to freshwater invertebrates. The guideline (850.1010) for acute toxicity testing is satisfied.

Acute Toxicity to Freshwater Invertebrates

Test Species	Test Material (% ai)	Toxicity Endpoint (mg ai/L)	Toxicity Category	MRID
Water flea (*Daphnia magna*)	73.62	EC50 = 1.5	Moderately toxic	455346-01 Acceptable
	76.1	EC50 = 3.3	Moderately toxic	429490-01 Acceptable
	89.8	EC50 = 3.7	Moderately toxic	473190-11 Acceptable

Freshwater Fish and Invertebrates, chronic

Two studies are available. NOAECs have been determined for both fish and aquatic invertebrates. No additional chronic data on the parent are needed for freshwater organisms (850.1300, 850.1400). However, once degradates have been identified in the Aerobic Aquatic Metabolism study (835.4300), any significant degradates that persist for more than one week may trigger the need for both of these chronic tests.

Chronic Toxicity to Freshwater Organisms

Species	Test material (% ai)	Toxicity (mg ai/L or kg)	Endpoint	MRID
Water column:				
Fathead minnow (*Pimephales promelas*)	89.8	NOAEC = 0.28 LOAEC = 0.59	Growth	477598-15 Acceptable
Water flea (*Daphnis magna*)	89.8	NOAEC = 0.91 LOAEC = 1.9 EC50 = 2.4	No. offspring; Immobility	477598-14 Acceptable

Estuarine/Marine Fish and Invertebrates, acute

The available studies categorize technical-grade BIT as being slightly toxic to estuarine/marine fish and moderately to very highly toxic to invertebrates. The guidelines for acute toxicity to estuarine/marine fish (850.1075) and invertebrates (850.1025, 850.1035) are satisfied.

Acute Toxicity to Estuarine/Marine Invertebrates

Test Species	Test Material (% ai)	Toxicity Endpoint (mg ai/L)	Toxicity Category	MRID
Sheepshead minnow *(Cyprinodon variegatus)*	76.1	LC50 = 12.2	Slightly toxic	429450-01 Acceptable
	89.9	LC50 = 19	Slightly toxic	477598-13 Acceptable
Mysid shrimp *(Mysidopsis bahia)*	76.1	LC50 = 0.99	Highly toxic	429490-02 Acceptable
	89.8	LC50 = 1.8	Moderately toxic	477598-11 Acceptable
Pacific oyster (*Crassostrea gigas)*	76.1	EC50 = 0.047	Very highly toxic	429524-01 Acceptable

Estuarine/Marine Fish and Invertebrates, chronic

No chronic data are available for estuarine/marine fish (850.1400) or mysids (850.1350). Because the acute toxicity to the estuarine/marine fish is less than that of the freshwater fish and the mysid is comparable to the daphnid, the Agency can use the acute: chronic ratio (ACR) from the freshwater species and the acute data to extrapolate the chronic NOAECs for the estuarine/marine organisms if values are needed for risk assessment.

Aquatic Plants

No data are available. To support the active ingredient, one green algae (*Selenastrum capricornutum*) study (850.4500) is required for this use pattern. If the EC_{50} of BBIT is less than 1.0 mg/L, studies are also required on three additional species (*Anabaena flos-aquae* (850.4550), *Navicula pelliculosa* (850.4500), and *Skeletonema costatum* (850.4500)).

Benthic Organisms

Based on environmental fate properties (K_d <50 L/kg, K_{oc} <1000, log K_{ow} <3), sediment toxicity testing (850.1735, 850.1740) is not needed.

Appendix C References

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44364913 Gilbert, J.L., Roberts, G.C. (1996) Acute Toxicity to Bluegill Sunfish (*Lepomis macrochirus*): Lab Project Number BL5701/B. Unpublished study prepared by Brixham Environmental Lab, ZENECA Specialties.

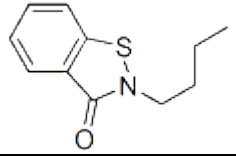
Appendix D Screening Level Down-the-Drain Analysis

No Down-the-Drain (DtD) analysis was performed for this FWP.

Appendix E Product Chemistry

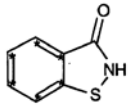
The chemical and physical property information for BBIT are summarized in Table E1, and for BIT are summarized in Table E2. Table E3 contains the chemical and physical properties of the BIT transformation products.

Table E1 – Physical-Chemical Properties for BBIT

Guideline No./ Study Type	Results	Reference
Chemical structure		None
Smiles code	O=C(N(CCCC)Sc1cccc2)c12	None
Molecular formula	$C_{11}H13N1O1S1$	N/A
Molecular weight (g/mol)	207.29	None
Water Solubility(mg/L)	418	EPI-Suite 4.11
830.7050 UV visible sorption	Absorption from 290-350 nm	MRID 48191702 Value for BIT
830.7370 Dissociation constant	Acid dissociation constant 9.12×10^{-8} moles/L (PAI) pKa 7.04 at 25 °C	MRID 43584001 Value for BIT
830.7550 Partition coefficient	2.32	EPI-Suite 4.11
830.7950 Vapor pressure (mm Hg)	9.97×10^{-6}	EPI-Suite 4.11
Henry's Law Constant (calculated) Atm m^3 mol^{-1}	6.5×10^{-9}	EPI-Suite 4.11

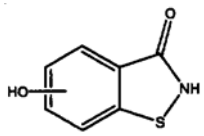
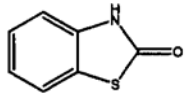
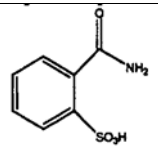
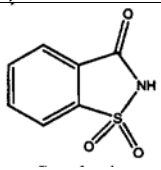
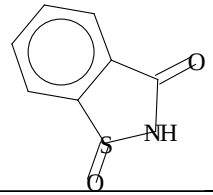
atm-m^3/mol = atmosphere cubic meter per mole; °C = degrees Celsius; mg/L = milligrams per liter; mmHg = millimeters of mercury

Table E2 – Physical-Chemical Properties for BIT

Guideline No./ Study Type	Results	Reference (MRID)
Chemical structure		None
Smiles code	O=C(NSc1cccc2)c12	None
Molecular formula	$C_7H_5N_1O_1S_1$	None
Molecular weight (g/mol)	151.19	None
Water Solubility(mg/L)	1,118 ppm at 20 ºC 1,380 ppm at 24 ºC	43584001
830.7050 UV visible sorption	Absorption from 290-350 nm	48191702
830.7370 Dissociation constant	Acid dissociation constant 9.12 x 10^{-8} moles/L (PAI) pKa 7.04 at 25 ºC	43584001
830.7550 Partition coefficient (log Kow)	1.4 (PAI)	43584001
830.7950 Vapor pressure (mm Hg)	1.14 x 10^{-6} mm Hg at 25 ºC	43584001
Henry's Law Constant (calculated) Atm m^3 mol^{-1}	1.64 x 10^{-10}	None (1.14 x 10^{-6} * 151.19)/(760 *1,380)

atm-m^3/mol = atmosphere cubic meter per mole; ºC = degrees Celsius; mg/L = milligrams per liter; mmHg = millimeters of mercury

Table E3 – Physical-Chemical Properties BIT Transformation Products from EPI-WEB 4.11

Guideline No./ Study Type	Compound				
	Hydroxy-1,2-benzisothiazol-3-one	**1,2-benzothiazolin-2-one**	**2-sulfobenzamide**	**Saccharin (1,2-benzisothiazoli-3-one-1,1-dioxide)**	**Bit-S-Oxide 1,2-benzisothiazoli-3-one-1-oxide)**
Chemical structure					
Smiles code	O=C(NSc1ccc(O)c2)c12	1cc(NC(=O)S2)c2ccc1	c1c(C(=O)N)c(S(=O)(=O)(O))ccc1	O=C(NS(=O)(=O)c1cccc2)c12	O=C(NS(=O)c1cccc2)c12
Molecular formula	$C_7H_5N_1O_2S_1$	$C_7H_5N_1O_1S_1$	$C_7H_7N_1O_4S_1$	$C_7H_5N_1O_3S_1$	$C_7H_5N_1O_2S_1$
Molecular weight (g/mol)	167.18	151.18	201.20	183.18	167.18
Water Solubility(mg/L)	1.77×10^5	2,354	1×10^6	789	27,400
830.7050 UV visible sorption	No data but expected to be similar to parent BIT	No data but expected to be similar to parent BIT	No data but expected to be similar to parent BIT	No data but expected to be similar to parent BIT	No data but expected to be similar to parent BIT
830.7370 Dissociation constant	No data	No data	No data	No data	No data
830.7550 Partition coefficient	0.16	1.76	-3.16	0.91	0.43
830.7950 Vapor pressure (mm Hg) at 25 °C	3.96×10^{-7}	5.41×10^{-6}	4.95×10^{-10}	1.03×10^{-7}	1.45×10^{-6}

Guideline No./ Study Type	Compound				
	Hydroxy-1,2-benzisothiazol-3-one	**1,2-benzothiazolin-2-one**	**2-sulfobenzamide**	**Saccharin (1,2-benzisothiazoli-3-one-1,1-dioxide)**	**Bit-S-Oxide 1,2-benzisothiazoli-3-one-1-oxide)**
Henry's Law Constant (calculated) Atm m^3 mol^{-1}	4.92×10^{-13}	4.57×10^{-10}	1.31×10^{-16}	3.15×10^{-11}	1.16×10^{-11}

atm-m^3/mol = atmosphere cubic meter per mole; ^oC = degrees Celsius; mg/L = milligrams per liter; mmHg = millimeters of mercury

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